THE COMMONWEALTH TRANS-ANTARCTIC EXPEDITION

MEDICAL AND PHYSIOLOGICAL ASPECTS OF THE ADVANCE PARTY

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THE Commonwealth Trans-Antarctic Expedition set out from London in November, 1955, and returned, its field tasks completed, in May, 1958 (Fuchs and Hillary 1958). The expedition had two distinct phases—the Advance Party and the Crossing Party. The aim of these two was directed at one object—to cross the Antarctic making observations on the way—but the conditions under which they lived were very different.

The " eight man " Advance Party, whose job it was to prepare a base and begin the scientific work, lived throughout their year in an unusually primitive fashion. Owing to delay in the ice, which caused them to arrive at their destination 5 weeks later than planned, the hurried withdrawal of the ship as soon as all the stores had been unloaded, and the loss of many of those stores when the sea-ice broke up, they were forced to live in inadequate shelter with too little fuel and to work outdoors throughout the polar night (Goldsmith 1957).

This expedition represented my first experience of the Antarctic, and so my judgments may well be different from those who are veterans in this field. On the other hand, the newcomer may sometimes make criticisms or observations which are valid just because he is a newcomer.

Working Conditions

Throughout the year nine out of ten days were spent working outdoors. The work consisted first in shifting stores and in transporting the hut sections and the most essential supplies from the landing-place to the base site two miles inland. Forklift attachments on the tractors would have been invaluable for this work (Lewis and Masterton 1955) as many of the loads were heavy. The men had to lift boxes weighing up to half a ton; equally unmanageable were small boxes containing 1 cwt. of bolts. This task completed, the hut had to be built (fig. 1)—its pre-cut sections weighed in all 60 tons, and their design was too complicated and worked to too fine a tolerance, so that with the unskilled labour available progress was slow—but for most of the time snow-digging in one form or another was the main occupation. For example, the prefabricated wall sections had to be dug out, which involved driving tunnels 70 yards long beneath the mounds of drift which covered them. The work was slow and laborious, for the drift snow had consolidated into a hard mass. When some of the panels had been put into the hut-frame, drift also filled the inside of the hut, and this too had to be dug out. Other stores—food, medical equipment, and meteorological and engineering stores—had all to be traced and uncovered as they were required. The engineer had to service the vehicles out-of-doors, handling heavy metal parts without gloves (fig. 2). The meteorologists erected and maintained their instruments and were successful in obtaining regular surface observations. The dogs had to be fed and cared for, and the sledges built and prepared for the summer journeys. Throughout the year slow progress was being made with the building of the hut, which still remained unfinished at the end. The men who worked in the only shelter available (the hut's shell and a small shack) had the benefit of being protected from the wind though not from the cold.

Fig. 1—The hut skeleton, designed to bear a great weight of snow, proved to be exceedingly difficult to erect.

Fig. 2—Servicing vehicles out of doors presented great problems. The sno-cat with its engine dismantled after a blizzard.

At first the party considered a temperature of −30°C and a wind of 20 knots the signal to retreat to the shelter of the crate in which they lived. But as the temperatures fell, without the wind speed decreasing, men were able to tolerate much worse conditions. One man assessed his comfort whilst digging at −45°C in a 17 knot wind as " comfortable ". No difficulty was experienced in breathing, nor was there any evidence of pulmonary damage from working at these low temperatures.

Some men became amazingly good at working in low temperatures with bare fingers (fig. 3). Nearly all managed to remove their gloves to handle tacks at −18°C, though only the carpenter was able to work in still air at −36°C with bare hands, and even he had to warm the handles of his tools and his hands frequently. The engineer dismantled an engine to replace a broken valve in a temperature well below 0°C. Although there was this obvious adaptation of the hands, the speed at which tasks could be done was much reduced. Even simple jobs took five or six times longer in the cold than they would have done in well-heated surroundings.

Living Conditions

For 9 months the party lived in the crate in which their ' Sno-cat ' had been shipped and which they had

assembled as soon as the ship had sailed (fig. 4). This box was 20 ft. long, 9 ft. high, and 7 ft. 6 in. wide. It was partly insulated with fibre-glass and had two small 'Perspex' windows, one at each end. In it the men cooked on three 'Primus' stoves and ate at a central table. One end housed the radio and its batteries, kept charged by a wind generator, while clothes were hung from the ceiling to dry. The crate was crowded, cold, and uncomfortable, and there was just enough room for the eight men to sit around the table. The fibre-glass insulation soon became soaked as a result of condensation, and frost formed on the inside of all walls (fig. 5). Once four inches of ice were chipped off a wall. The temperature in the crate rarely rose above 7°C, whilst the floor and ceiling were fortunately usually below freezing-point, because when the ceiling temperature rose above this point the frozen condensation melted and dripped on to the occupants. Ventilation was an acute problem. The fumes from the two paraffin heaters and the three primuses fouled the air. Many times matches would not remain alight, and the occupants often showed symptoms of carbon-monoxide poisoning—headaches, nausea, and vomiting. Conjunctivitis due to the irritant primus fumes was not infrequent. It was no solution to let in cold air through vents, as this made the crate too cold to live in and drift snow entered by any opening. As the crate became completely buried so the ventilation problem became even more difficult. At the end of 9 months the crate was abandoned and the move was made into one room of the main hut, the remainder of which was still full of snow.

Fig. 3—The engineer handling his tools with bare hands at a temperature below freezing-point while servicing a tractor.

Washing and toilet facilities were non-existent, but this did not seem to give rise to any ill effects. Indeed, when eventually the relief ship arrived offering limitless hot water, the members of the Advance Party were noticeably reluctant to take advantage of it.

Fig. 4—Shelter was at first provided by tents and the re-erected sno-cat crate.

Food

The men took turns at cooking for 4 days at a time. This, on balance, is the most satisfactory arrangement, for it avoids monotony and also gives the men an enforced change of occupation in a part of the world where each day tends to be like every other. The food was tinned or dehydrated; it was adequate but uninteresting. At first it was cooked on primuses, but after some months a five-gallon oil drum was converted into an oven (fig. 6) and the scope and skill of the cooks increased so that by the end of the year the cooking was much more varied. The men's body-weights, in contrast to those reported on other expeditions (Lewis et al. 1956), fell or remained steady and showed no rise in the winter months. This rise previously reported is almost certainly due to the inactive life during the polar night and not to any function of cold acclimatisation. Fat-thickness measurements mirrored these changes closely.

Clothes

The clothes the men wore were basically the same as those developed by the Falkland Islands Dependencies Survey in Graham Land. They consisted of layers of relatively normal clothing—i.e., Army shirts, pullovers, and trousers, seamen's stockings and jerseys, and outer windproof coverings. Despite the tearing of clothes and the cracking of boots the party did manage to remain reasonably comfortable, although the same clothes were worn continuously for many months. There were no facilities to launder clothes, so that all articles became increasingly dirty and greasy. Sometimes when socks were changed they were found to contain an almost perfect cast of the foot made of an accumulation of stratum corneum. Perspiration, in cold climates, condenses readily within the layers of clothing so that drying is most important. As the clothing was dirty and there was insufficient fuel, it dried very slowly. Complaints of

Fig. 5—Water being made from blocks of snow melted in a dustbin. Note the frost on the fibre-glass quilted wall.

cold hands and feet were thus often due to damp gloves or socks. Clothes lost much of their insulation value as they became worn. Nevertheless, weekly records show a decline in the amount of clothing worn for similar climatic conditions at the end of the year compared with the beginning. This is a possible indication of a general acclimatisation (Goldsmith, unpublished).

Sleep

The men slept in four two-man tents which were pitched round the crate. These were the traditional black, double-skinned, sleeve-entrance type of polar tent. They were occupied for 9 months, during which they withstood the worst the weather could do without sustaining any serious damage. Inside the tents the men slept in double-down bags laid on sheepskins on the snow, but later low canvas bed-frames were made. The tents were

Fig. 6—Cooking was done on three primuses, one of which was fitted with a rudimentary oven. The kitchen in the main hut.

unheated except on going to bed and getting up, so that the temperature in them was only a degree or two higher than that outside. As a result, the sleeping-bags soon became wet and icy from perspiration and condensation from the breath, thus losing much of their insulation; and, although the men went to bed fully clothed, with two extra blankets inside the bag, they still felt cold. Sleep records, which were kept throughout the year as part of the physiological programme, indicate the state of the sleeping-bag by the number of times men woke up during the night. There is, however, good evidence that the men did get accustomed to sleeping in the cold. In the unheated cubicles of the hut, where the men slept for the last three months, temperatures of 0°C did not prevent them from sleeping in a single-layer unzipped bag, wearing only cotton pyjamas. There was, however, great individual variation. The carpenter, for instance, who showed a remarkable degree of local acclimatisation of the hands, found sleeping in a tent too uncomfortable and took to sleeping on a narrow wooden form in the relatively warm crate.

Medical Aspects

Despite the rigorous conditions, the ample medical equipment provided was seldom used. Special care had been taken to supply everything which it was thought might be required, due regard having been taken of the experience of others. The medical supplies were most beautifully packed and catalogued. Very little damage resulted from these stores being left in the open all winter, and even the box of goods rather optimistically labelled "Do not freeze" came to little harm. Yet even so there were deficiencies. For instance, five varieties of antibiotics were supplied but no throat lozenges! It is a mistake to concentrate on providing the more esoteric remedies and to omit the simplest.

Some of the special hazards encountered, such as carbon-monoxide poisoning and primus-fume conjunctivitis, have already been mentioned. Complaints directly attributable to the cold were all minor, such as lesser degrees of frostbite of face and fingers, and were never troublesome. Fingerpads appeared to thicken and often cracked, taking many weeks to heal. Small cuts and abrasions on the hands also healed very slowly. In the first few months some of the men suffered from aching pains and stiffness in the finger-joints, which was accompanied by some swelling of the joints without reddening. This condition, which has recently also been reported from American personnel at the South Pole (P. A. Siple, personal communication), was worse in the mornings and improved as the day went on. In one case it progressed to a condition similar to trigger-finger, but eventually resolved without treatment.

Infections of any kind seldom appeared. During the early part of the winter there were a number of cases of sore throat with partial loss of voice; but these did not seem to be infectious, there being neither pyrexia nor malaise with the quite severe pain. They may have resulted from inhalation of very cold air. There were no cases of the common cold during the year, and even when the relieving party arrived there was no generalised outbreak such as has so often been previously reported.

Among other conditions met was a case of pediculosis. This was unpleasant in a closed community, especially as the medical equipment included no insecticide. Disinfestation of the clothing was no problem as hanging the garment in the open was enough to kill all parasites (Nansen 1898); paraffin oil proved fatal to those on the skin and was not too irritant. Another man had symptoms of acute peptic ulceration, and it was difficult to treat him in the traditional fashion in a place where bed rest involved lying in a tent at −30°C and where the nearest approach to a white-diet was herrings in tomato sauce. There were numerous cases of severe chronic indigestion, although the diet did not contain an excessive amount of fat. Antacids, of which there was a good supply, were in fact the most frequently required medicament.

It was expected that accidents might be more frequent in the cold than in temperate zones, but this was not found to be so. Torn muscles, a badly bruised hand, a subconjunctival hæmatoma due to a blast of oxygen from a cylinder, an embedded glass splinter, and minor cuts did not keep the men from work. In the whole year only one man-day was lost from illness. This compares very favourably indeed with other expeditions. In circumstances where being sick is so uncomfortable, illness tends to be ignored.

There was little opportunity and no great need for any dental work. All members of the party had had thorough dental checks before leaving England, and none developed serious dental disease. There does, however, seem to be

Fig. 7—Dentistry under difficulties in the crate. The man on the left is holding the paraffin light, while the one on the right is preparing to leave the crate. Note the clothes hanging from the ceiling and the background of frost on the wall.

some evidence from dental examinations on return to this country that fillings deteriorate in the cold and that caries continues at least as fast, if not faster (fig. 7).

There are often serious personality clashes amongst members of small isolated communities. This isolated party of eight, however, living under unusually rigorous conditions, experienced no such troubles. This happy state of affairs may be attributed in part to the very rigour of the living conditions and also to the paternal, but not over-bearing, leadership. That is not to say there were no differences of opinion, but these differences never assumed serious proportions.

Physiology

The problems of the physiologist/medical officer on expeditions are quite similar to those of a newcomer to an old-established firm. Surveying, geology, and geophysics

Fig. 8—Fat-thickness measurement. The operator is wearing normal indoor clothing consisting of a nylon fur-lined anorak.

are traditional polar scientific pursuits, but the study of man is something new and not yet automatically accepted. It is therefore the physiologist's function first to sell the idea of physiology to the organisers of such an enterprise, and then to sell it to those who must inevitably be his subjects. He must make all the necessary observations himself and not delegate the making and recording of such observations to the subjects. The physiologist who wishes to get the maximum cooperation from his fellow expedition members should always be willing to help in the general work of the expedition.

For the Commonwealth Trans-Antarctic Expedition a programme of research on the men and their environment was planned by the Division of Human Physiology of the Medical Research Council, based on work previously done on other polar expeditions. Observations such as the recording of body-weight, skinfold thickness (fig. 8), clothing, sleep, and indoor climate were made, the results of which have already been briefly indicated. These investigations, necessarily simple, were all directed to eliciting evidence for the existence and the mechanism of acclimatisation to cold.

It is rare on a modern polar expedition to be able to make observations on men exposed to intense cold for long periods, because of the ample provision of material comforts. The Commonwealth Trans-Antarctic Expedition, however, owing to its special circumstances, provided a very fruitful opportunity for such investigations.

Conclusions

The Advance Party of the Trans-Antarctic Expedition lived under extremely difficult conditions and were exposed to cold stress as severe as any that has been experienced. The eight men suffered no serious illnesses, nor was there any sign that the rigorous life they led left any permanent ill effects. There was clear evidence, however, that they did become acclimatised in numerous ways to the extreme cold. Possibly, because of the long exposure to cold, they acquired a degree of acclimatisation which was greater than is usual for polar conditions.

As a consequence of the loss of stores and the primitive conditions under which they lived, the party were able to test their equipment most thoroughly. In this paper, only such matters as are related to the human aspects have been described.

In polar work there is a strong tradition of insularity and parochialism, and mistakes are too often made through taking only scant notice of the experience of others; but, above all, polar expeditions from the earliest times have always been subject to limitations in time and money. It is worth emphasising that the men on this expedition were exposed to an unusually prolonged and severe degree of cold. In spite of this and the hazards of carbon monoxide, they remained in remarkably good health. Because of mishaps it was not possible to carry out the programme of physiological work which had been planned. Evidence of acclimatisation was, however, obtained from the detailed clothing records. Fat thickness and weights were measured regularly, and some assessment was made of food intake.

Despite mishaps, the expedition achieved its objects; and this achievement, together with its scientific results, will stand as its justification.

REFERENCES

Fuchs, V. E., Hillary, E. (1958) The Crossing of Antarctica. London.
Goldsmith, R. (1957) *St. Bart's Hosp. J.* **61**, 288.
Lewis, H. E., Masterton, J. P. (1955) *Lancet*, ii, 494, 549.
— — Rosenbaum, S. (1956) *Abstr. int. physiol. Congr.* p. 565.
Nansen, F. (1898) Farthest North; vol. 1, p. 175. London.

PROFOUND HYPOTHERMIA

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AT the present time visual intracardiac surgery may be achieved by the use of either a pump-oxygenator or hypothermia. A combination of the two methods, with cooling to 30°C, has been tried experimentally by several investigators, and clinically by Sealy et al. (1958). Hypothermia lessens the demand on the pump-oxygenator during cardiopulmonary bypass, because the body's oxygen requirements are smaller and can be met by a lower blood-flow.

When hypothermia is used by itself the customary limit of cooling is 28–30°C. At this level of temperature circulatory arrest and open heart surgery is possible for eight to ten minutes only: after this time there is considerable risk of permanent cerebral damage. Cooling to lower temperatures has been regarded as unwise because it often causes irreversible ventricular fibrillation. The use of antifibrillation drugs has not yet improved the position. There is much experimental evidence, however, to show that mammals (non-hibernating as well as hibernating) can survive profound hypothermia.

Anjus and Smith (1955) cooled rats to 1°C and rewarmed them to recovery. Smith et al. (1954) showed that golden hamsters can survive supercooling to −5·5°C, despite partial crystallisation of body fluids, and complete arrest of recordable body function for some hours. Gollan et al. (1955) combined the use of a pump-oxygenator and a heat-exchanger to cool dogs to 0°C with survival.

In dogs subjected to surface cooling, Bigelow et al. (1950) showed that, down to the point of cardiac arrest, which was usually between 18° and 22°C, the relation between oxygen consumption and temperature was almost linear. At 20°C oxygen consumption was 15% of normal. By extrapolation of the curve they deduced that somewhere between 10° and 12°C oxygen consumption would be minimal. At these low temperatures circulatory arrest might be tolerated for a long time, provided both the body temperature and circulation could be restored.

Niazi and Lewis (1958) have recently reported the case of a woman with widespread malignant disease whose temperature was reduced to 9°C by surface cooling, with cardiac arrest for forty-five minutes, and who recovered her normal body temperature without harm.

Investigation

This paper describes some of our work on profound hypothermia in dogs. It arose out of some experiments—at first unconnected with hypothermia—in which we studied the feasibility of bypassing the left ventricle during operations on this chamber.

To achieve this, a cannula was inserted in the left atrium, and blood was collected by siphon drainage into a reservoir, from which it was pumped into the femoral artery. Cooley and DeBakey (1957) have used a similar method to bypass aortic aneurysms during resection and graft replacement.

We considered the effect of producing cardiac arrest under these conditions. Would blood, returning to the right atrium, flow through a non-functioning right ventricle, through the low-pressure pulmonary vasculature, and, aided by the pumping effect of artificial respiration, find its way into the left atrium? We tested this by cooling the blood in its extracorporeal course, because we knew that hypothermia eventually stops ventricular function because of fibrillation or asystole. In a small series of experiments, fibrillation occurred at about 22°C as recorded in the pharynx; left atrial return was variable, sometimes ceasing very quickly, sometimes continuing for several minutes before gradually decreasing in amount. We also hoped that, if the load on the left ventricle was diminished, by its partial bypass, the heart might continue to beat regularly at lower temperatures. This was not so.

It appeared that, to achieve profound hypothermia by blood-stream cooling, it would be necessary to take over the function of both ventricles by mechanical means, particularly when fibrillation or asystole had occurred. In this way we might be able to (1) establish a satisfactory pulmonary and systemic circulation; (2) continue the cooling process in the presence of a non-functioning heart; (3) rewarm when desired; and (4) restore normal heart action.

Experimental Method

The extracorporeal circuit (fig. 1) contained two reservoirs—one to collect pulmonary venous blood from the left atrium,

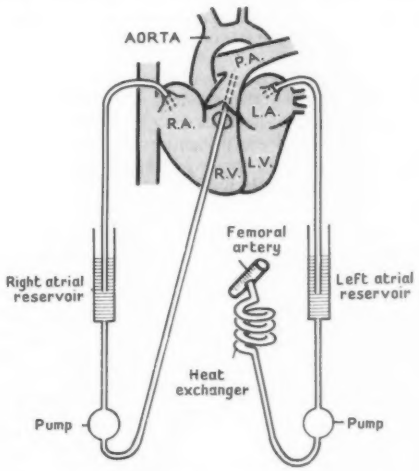

Fig. 1—Diagram of experimental circuit.

and the other to collect systemic venous blood from the right atrium.

Blood from the pulmonary venous or left-atrial reservoir passed through a cooling coil, and then returned to a femoral artery through one head of a 'Sigmamotor' pump unit. Blood from the sytemic venous or right-atrial reservoir was pumped through the other head into the pulmonary artery, via a cannula inserted through a stab incision in the infundibulum of the right ventricle. Systemic venous blood was not cooled. The heat-exchanger consisted of 100 ft. of polyvinyl ethylene chloride tubing (1/4 in. internal diameter)—poor material for heat exchange, because of its low conductivity, but easy to obtain and convenient to use. This was immersed in a refrigerant mixture of methyl alcohol and carbon-dioxide snow maintained at 2–4°C. The apparatus was primed with 2–3 pints of fresh heparinised blood.

In half the experiments in which this circuit was used, a stainless-steel filter and a bubble trap were placed proximal to the femoral cannula.

Surgical Technique

Mongrel dogs of 8–15 kg. were used. Each was anæsthetised with thiopentone and succinylcholine, and maintained on nitrous oxide and oxygen from an automatic respirator. In later experiments a mixture of 95% oxygen and 5% carbon-dioxide was used. The femoral artery was first mobilised but not cannulated. The chest was opened by bilateral trans-sternal thoracotomy or median sternotomy. Heparin, 1·5 mg. per kg., was given, and the femoral artery cannulated.

A catheter as large as possible was inserted into the left atrium and connected by the pulmonary venous line to the left-atrial reservoir. The appropriate pump was then started, with partial left-ventricular bypass and cooling. Cooling was so rapid that the right atrium required immediate cannulation, and connection to the systemic venous line and right-atrial reservoir. The pulmonary-artery cannula was inserted as soon as left-atrial drainage began to diminish at the onset of heart-failure, and the pulmonary circulation was begun. Systemic flow could be varied by means of the pump transmitting blood into the femoral artery. This pump was calibrated before each experiment. The arterial flow determined the amount of systemic venous return, and the pulmonary flow could be adjusted to keep the reservoir levels constant. Little adjustment was needed once the levels were stabilised, and this was quickly achieved. Regurgitation through the pulmonary valve with the cannula in situ did not occur.

Twelve experiments were carried out, with flow-rates varying from 50 to 70 ml. per kg. per minute. In ten experiments rewarming was started as soon as a pharyngeal temperature of about 10°C was reached: in two others a period of circulatory arrest of thirty minutes was allowed. For rewarming, water at 40–44°C was substituted for the refrigerant solution. When the pharyngeal temperature had risen to about 30°C a single electric shock was sufficient to restore regular rhythm in the fibrillating heart, and at this stage right-ventricular bypass was discontinued. Shortly afterwards left-ventricular bypass was stopped, and the cannulæ were withdrawn. Protamine sulphate was then given, 3 mg. per kg., to neutralise the effect of heparin. Surface cooling and warming was not used, and no attempt was made to control room temperature.

The following data were obtained:

1. Central aortic pressures were recorded via a catheter introduced into the femoral artery. Continuous tracings with an electroencephalograph (E.E.G.) and electrocardiograph (E.C.G.) were made.

2. Pharyngeal, rectal, mediastinal, and intraperitoneal temperatures were recorded with thermistors and a multichannel recorder.

3. Blood analyses included arterial and venous oxygen saturation, and estimation of plasma hæmoglobin and electrolyte concentrations.

Results

The significance of some observations is speculative, but some are worthy of note.

It was always possible to cool from 37° to 8°C (pharyngeal temperature) in about twenty-five to thirty minutes. Rewarming was a little slower (fig. 2). In a separate experiment to investigate the relationship between pharyngeal and cerebral temperature, an animal was cooled to a pharyngeal temperature of 8°C, with thermistors placed as before, but with an additional needle electrode in the brain. In this experiment the temperature fell more slowly than usual (fig. 3). The brain temperature lagged 4°C behind the pharyngeal temperature above 21°C, but at lower temperatures this difference fell to between 2° and 2·5°C. This showed that the brain was not excluded from the cooling process. The difference in brain and pharyngeal temperature may be attributable to hæmatoma formation around the needle thermistor in a heparinised animal. In another experiment, where the brain needle was placed in the subdural space between the cerebral hemispheres, the gradient was about 1°C.

Plasma-electrolyte changes were not significant. Arterial oxygen saturation was always in the region of 98%, and venous

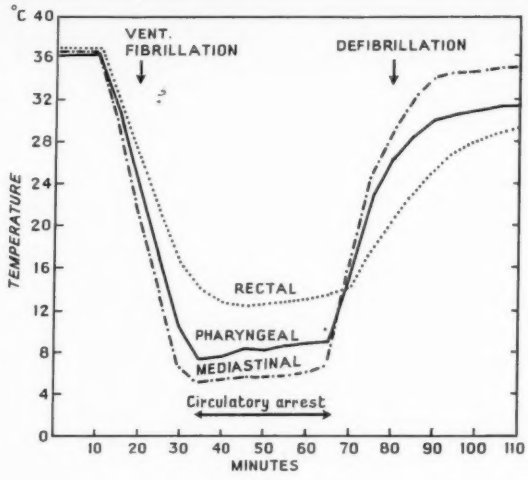

Fig. 2.

oxygen saturation increased with cooling to as much as 85% at 8°C.

The mean blood-pressure was usually between 80 and 130 mm. Hg with flows of 50 to 70 ml. per kg. per minute. The E.E.G. became isoelectric at about 20°C, and the E.C.G. underwent changes characteristic of cooling, bradycardia being followed by varying degrees of heart-block culminating in ventricular fibrillation. Atrial fibrillation was not observed; occasionally the atria continued to beat at a slow rate in the presence of ventricular fibrillation.

Two animals died because of our inexperience with the method. Of the others all recovered to the point of normal respiration and reflexes, and some to consciousness. All but two, however, died up to twenty-four hours later. The two survivors had a total period of ventricular fibrillation lasting about one hour, during which time the pumps maintained a circulation. They made complete recoveries without evidence of neurological damage. In the others no cause of death was apparent at postmortem examination, but, whereas the survivors had plasma-hæmoglobin values of 40 and 45 mg. per 100 ml., the non-survivors had levels above 100 mg.

Comment

The high mortality in this series was disappointing, but the survivors were proof that, using the method

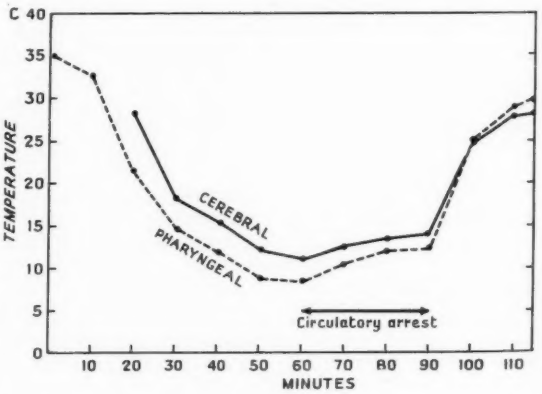

Fig. 3.

described, it is possible to cool a dog to 8°C, and rewarm it, without harm.

The deaths were similar to some we had seen following cardiopulmonary bypass using the pump-oxygenator of Lillehei and de Wall, and were probably associated with cerebral damage which might have been produced in several different ways. It may have resulted from defects in the extracorporeal circuit causing gaseous or particulate emboli—although at necropsy the cerebral vessels appeared to be normal, and contained no obvious gas bubbles. A hundred feet of plastic tubing in the heat-exchanger was a considerable resistance to blood-flow: on one occasion this exceeded 750 mm. Hg, and was clearly undesirable.

In some experiments a fall in blood-pressure had been observed when partial left-ventricular bypass and cooling were started. Although this was eventually corrected, such a period of hypotension in the early stages of the experiment, when the body temperature was normal, would affect the final results. As the flow-rates used would have been adequate at normal body temperature during cardiopulmonary bypass using a heart-lung machine, the deaths are unlikely to have been due

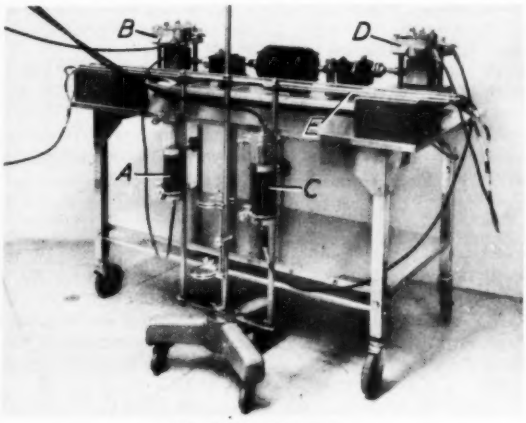

Fig. 4—The apparatus.

(*A*) Right atrial reservoir. (Systemic venous blood enters at top.) (*B*) Roller pump transmitting blood from this reservoir to pulmonary artery. (*C*) Left atrial reservoir. (Pulmonary venous blood enters at top.) (*D*) Roller pump transmitting blood from this reservoir to aorta via (*E*) stainless steel tubes arranged in parallel. (These are normally suspended in a trough through which hot or cold liquids are passed to effect heat exchange.)

to an inadequate circulation. The high systemic venous oxygen saturations at low temperature seem to show that flow was adequate; on the other hand there could be some interference with oxygen utilisation apart from the effect of cold. The ideal flow-rate was difficult to assess. It seemed logical to suppose that it could be decreased as the temperature fell, in step with the fall in tissue demand for oxygen. Under the conditions of these experiments, however, the circulating blood was discharging an additional function—that of a secondary refrigerant. A flow-rate exceeding the body's requirements may have been used in some phases of the experiment, because of the necessity for rapid cooling and rewarming.

Some features of the work encouraged us; although difficult at first in small hearts, the cannulations became easy with experience: cannulation of the left atrium is the most difficult, while that of the pulmonary artery is the easiest. There was no difficulty in getting venous return to the reservoirs, or in effecting a balance between the levels.

There were no postoperative lung complications, even minor ones; this is in contrast to our experience with cardiopulmonary bypass, when we frequently observed bloodstained bronchial secretion (Drew et al. 1957). There was never any difficulty in restoring the heart to normal rhythm. There was no plasma-electrolyte disturbance.

Further Experiments

In the next series of experiments the apparatus was modified as follows (fig. 4):

The heat-exchanger consisted of four stainless-steel tubes ($^1/_4$ in. internal diameter), each of which was five feet in length and highly polished on the inside. They were arranged in parallel, and connected together with Y-shaped stainless-steel connectors and short lengths of polyvinyl ethylene chloride tubing. This arrangement was preferred to a coil because it offered less resistance and the straight tubes were easy to clean. The tubes were suspended in a trough through which cooling or warming liquids were passed from two reservoirs. The temperatures of these were kept at 2° and 45°C.

The sigmamotor pump-heads were discarded in favour of others of DeBakey type, which were designed and constructed in our laboratory. In-vitro experiments (to be published) showed that these gave consistently low hæmolysis-rates. It was decided to discard the filter.

To prevent sudden hypotension at the onset of partial left-ventricular bypass, an adjustable clip was placed on the pulmonary venous line, so that drainage from the atrium could be controlled by the surgeon. The flow of chilled blood into the aorta was started slowly, and increased to its maximum of 50–70 ml. per kg. per minute at the onset of right-ventricular bypass. The rate of increase in flow through the extracorporeal circuit was governed by the blood-pressure which was kept at an arbitrary mean of 80 to 100 mm. Hg.

Results

In four experiments cooling was carried out to 15°C, followed by a period of complete circulatory arrest lasting twenty to forty-five minutes before rewarming. Two animals survived without evidence of neurological damage.

One died after six hours from hæmorrhage, but, after operation had stood upright, and appeared to be normal neurologically. The fourth animal was hypertensive before operation, failed to recover consciousness, and at necropsy was found to have enlarged and grossly diseased kidneys.

In three of the four experiments, plasma-hæmoglobin was so little in amount that there was no difference in colour between samples taken before and after the experiment. This showed that the extracorporeal circuit was improved, and resolved previous fears that the fragility of red blood-cells might increase unduly if they were exposed to trauma at temperatures as low as 2°C, and as high as 45°C.

Summary and Conclusions

A small number of experiments was sufficient to show that, using simple apparatus, it is possible to induce profound hypothermia in a dog, followed by complete circulatory arrest for thirty minutes, and then to rewarm it with recovery.

Many colleagues helped in this investigation. Our thanks are due to Dr. Percy Cliffe, Mr. D. M. Forrest, and Mr. John Gooden for the design and construction of the pumps used in the latter part of this work; to Mr. R. E. Trotman who devised the temperature recording apparatus; and to Mr. W. S. James, our laboratory technician. Miss Joan Smith provided unstinted secretarial help. Dr. Peter Hansell of the photographic department was responsible for the illustrations.

REFERENCES

Anjus, R. K., Smith, A. U. (1955) *J. Physiol.* **128,** 446.
Bigelow, W. G., Lindsay, W. K., Harrison, R. C., Gordon, R. A., Greenwood, W. F. (1950) *Amer. J. Physiol.* **160,** 125.
Cooley, D. A., DeBakey, M. E. (1957) *Ann. Surg.* **146,** 473.
Drew, C. E., Cliffe, P., Scurr, C. F., Forrest, D. M., Pearce, D. J., King, P. A., Coles, H. M. T., Leveaux, V. M., Zilva, J. F. (1957) *Brit. med. J.* ii, 1323.
Gollan, F., Phillips, R., Grace, J. T., Jones, R. M. (1955) *J. thorac. Surg.* **30,** 626.
Niazi, S. A., Lewis, F. J. (1958) *Ann. Surg.* **147,** 264.
Sealy, W. C., Brown, I. W., Young, W. G. (1958) *ibid.* p. 603.
Smith, A. U., Lovelock, J. E., Parkes, A. S. (1954) *Nature, Lond.* **173,** 1136.

PROFOUND HYPOTHERMIA IN CARDIAC SURGERY

REPORT OF THREE CASES

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THE technique of inducing profound hypothermia described in the preceding paper was carried out in animals with normal hearts. It depended on the ability to direct part (eventually most) of the systemic and pulmonary venous streams from the atria into reservoirs, from which the blood was pumped respectively into the aorta and the pulmonary artery.

In the presence of a septal defect—especially a large one at atrial level—this might present some difficulty, particularly in the early stages of the cooling process. On the other hand it had been observed that, later on, the oxygen saturation of systemic venous blood became so high that mixing of pulmonary and systemic blood would no longer be so important. Whether the technique would in fact prove satisfactory in such cases was a question which would be difficult to answer in the laboratory.

With this in mind, we chose as our first patient a child with a large atrial septal defect, whose condition would be considered inoperable by other techniques.

Case-reports

FIRST CASE

The patient was a mongol, aged 12 months and weighing 13½ lb., with multiple abnormalities. He remained in hospital after birth and had recurrent bouts of cardiac failure, for which digitalis was given. The clinical signs, electrocardiography, cardiac catheterisation, and dye-dilution studies suggested persistence of the atrioventricular canal, possibly complete.

Operation

Anæsthetic.—Premedication was with pethidine and atropine. Induction was with halothane, and after tracheal intubation anæsthesia was maintained with nitrous oxide, ether, and very small doses of tubocurarine.

During cooling and rewarming 95% O_2 and 5% CO_2 was given.

Surgical techniques.—Incisions were made in both groins and the femoral arteries mobilised. A catheter was introduced into one of the vessels for continuous observations on the central aortic pressure. During this period the blood-pressure was low with a mean of about 50 mm. Hg.

The chest was entered by median sternotomy. Incision of the pericardium revealed a large heart of poor colour and feeble action. The right atrium was grossly dilated. The femoral artery was cannulated, and heparin, 1·5 mg. per kg., was given. Two cannulæ were inserted into the right-atrial appendage, one pointing towards the left atrium and the other towards the mouth of the inferior vena cava. The cannulæ were connected to their respective venous lines and partial left-ventricular bypass begun.

The initial extracorporeal flow was 150 ml. per min., and the clip on the venous line was adjusted to keep the left-atrial reservoir level constant. Cooling was then started. 15 minutes later, when the heart had slowed considerably, a pulmonary-artery cannula was inserted through the infundibulum of the right ventricle, and right-ventricular bypass instituted. The extracorporeal flow was then 450–500 ml. per min. with a mean blood-pressure of about 80 mm. Hg.

It took 27 minutes for the pharyngeal temperature to fall to 15°C. The pumps were then stopped, and the venæ cavæ, aorta, and pulmonary artery were occluded by snares. Drainage from the atrial cannulæ was allowed to continue until the heart was emptied of blood. The venous lines were then clamped.

A long incision in the right atrium revealed a large ostium-primum type of defect. At the lower limit of the defect the aortic cusp of the mitral valve continued over the upper margin of the ventricular septum, and appeared to merge with the medial cusp of the tricuspid valve (fig. 1). This unusual abnormality made it difficult at this stage to decide whether a ventricular septal defect was in fact present. The aortic cusp of the mitral valve was bifid. There was rather more atrial septum superiorly than is usual with a persistent ostium primum, and this showed one large defect and another which was fenestrated.

The left-atrial cannula was now removed, and reinserted through the left-atrial wall between the pulmonary veins on the right side, so that when the defect was closed the cannula would be in its correct position draining pulmonary venous blood.

The two smaller defects in the superior part of the septum were then closed, and the aortic cusp of the mitral valve was repaired (using interrupted silk sutures). It was possible to correct the ostium-primum defect by direct suture between its anterior and posterior margins. The inferior part, however, presented some difficulty, and in this area sutures were placed in the aortic mitral cusp as it crossed from left to right above the ventricular septum.

As the repair proceeded, the cardiac chambers were refilled with blood. When, eventually, all air had been excluded from the heart, the right-atrial incision was closed.

There was a period of complete circulatory arrest lasting 46 minutes, during which time the pharyngeal temperature had risen to 20°C.

The pumps were then started and rewarming began. Ventricular fibrillation did not occur, and during the period of intracardiac surgery the heart was beating with slow, irregular, weak contractions. Rewarming was rapid, and very soon the heart was beating strongly in sinus rhythm. Its colour improved, and 23 minutes after rewarming had begun the temperature was 32°C. The artificial pulmonary circulation was now discontinued. 4 minutes later left-ventricular bypass was abandoned, and all the cannulæ were removed from the heart. The temperature was then 33·5°C.

Protamine sulphate, 3 mg. per kg., was given and the arterial cannulæ were removed with repair of the femoral artery. The pericardium was closed and the chest incision was closed with drainage of the mediastinum.

Fig. 1—Heart from case 1 seen from left ventricle showing: (A) sutures in bifid aortic mitral cusp; (B) chordæ from this cusp passing across the edge of ventricular septum to the right ventricle.

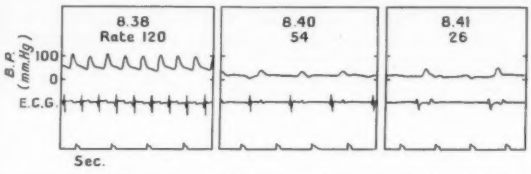

Fig. 2—Record from case 1, showing sudden heart-block with fall in blood-pressure.

Postoperative Course

70 minutes after the chest had been closed the infant was breathing spontaneously, moving all four limbs and swallowing. The pupils were small and equal and reacted to light, and lid reflexes were present. However, 45 minutes later the heart-rate suddenly fell, and continued to fall (fig. 2) with a simultaneous fall in the blood-pressure. The chest was reopened, cardiac massage was started, and a vain attempt to combat the heart-block was made using a pacemaker.

Necropsy

Postmortem examination confirmed our appreciation of the intracardiac defect. Although the communication between the left and right sides of the heart had been greatly decreased, there was a significant unclosed ventricular septal defect. The preoperative diagnosis of persistent atrioventricular canal of the complete type was thus upheld.

Despite the fatal outcome this case had some encouraging features. Pulmonary and systemic venous return had been achieved despite the presence of a large communication between the left and right sides; and even in this infant's small heart it had proved possible to make the necessary cannulations. Cooling and rewarming had been without difficulty, and despite the long period of circulatory arrest there had been every indication of ultimate recovery until heart-block supervened. Moreover the heart had shown an improved action following intracardiac surgery. Plasma-electrolytes at the close of rewarming had hardly changed from preoperative values, and hæmolysis was negligible.

Contrary to our experience in the laboratory, ventricular fibrillation did not occur.

SECOND CASE

This patient was a high-grade mongol boy, 4 years of age, weighing 27½ lb. When the child was 3 months of age we had closed a patent ductus arteriosus. Cardiac catheterisation showed a ventricular septal defect with increasing pulmonary hypertension.

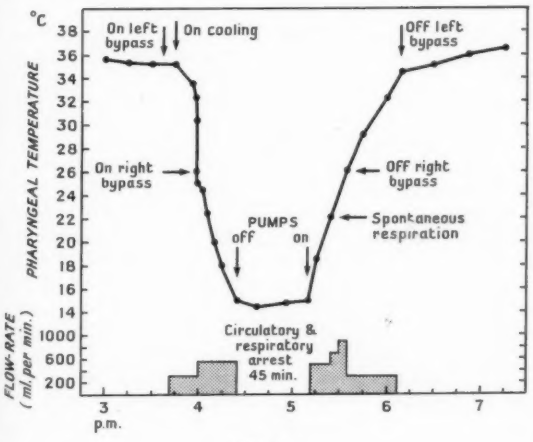

Fig. 3

The technique for cooling and rewarming was as in the first case, except that the two atria could be cannulated separately from the beginning. However, dilatation of the right atrium suggested an atrial septal defect, and the oxygen saturation of blood taken from the venæ cavæ, right atrium, right ventricle, and the pulmonary artery confirmed the presence of both atrial and ventricular septal defects. The right atrium was too small for digital inspection.

Fig. 3 shows graphically the essential details of cooling and rewarming. The circulation was suspended at 15°C, and the heart was emptied as before.

A long incision was made in the right atrium and a septal defect of secundum type about 2–3 sq. cm. in area was repaired. The incision in the atrium was closed.

A right ventriculotomy incision was then made after withdrawing the pulmonary-artery cannula. At first the defect in the ventricular septum was difficult to localise because it was completely hidden by the medial cusp of the tricuspid valve. However, its position was disclosed when each infrequent cardiac contraction caused ballooning of the cusp by blood from the left ventricle.

The cusp had to be incised before the defect high in the septum could be obliterated (five interrupted silk sutures were used). The cusp was then repaired. The heart was filled with blood, the ventriculotomy incision closed, and the pulmonary-artery cannula replaced. The period of total circulatory arrest lasted 45 minutes.

As in the previous case, ventricular fibrillation did not occur, and the heart-rate and vigour were rapidly restored on rewarming. Spontaneous respiration occurred at 22°C.

This child made a rapid uneventful recovery. Plasma hæmoglobin was again negligible and there was no significant plasma-electrolyte change. Cerebral function after operation appeared to be unimpaired and renal function was normal.

THIRD CASE

The patient was a boy, 2½ years of age, weighing 28½ lb., who suffered from recurrent respiratory infections. The clinical diagnosis of ventricular septal defect was confirmed by cardiac catheterisation which showed mild pulmonary hypertension associated with a pulmonary/systemic flow ratio of 2/1.

A similar procedure was followed. Cooling took place more slowly and a pharyngeal temperature of 15°C was reached in 45 minutes. This went down to 13°C during the 25 minutes of circulatory arrest.

The left atrium was large because of the increased pulmonary venous flow and was easy to cannulate. Right ventriculotomy disclosed a defect which was partly hidden by the medial cusp of the tricuspid valve (this was closed by three silk sutures).

Rewarming took 40 minutes, and the extracorporeal flow varied between 150 and 700 ml. per min.

This child was talking 30 minutes after the chest was closed. Once again, the heart did not fibrillate. The postoperative course was as uneventful as in the previous case.

Conclusions

Using the technique described it is possible to achieve profound hypothermia in children. At 15°C it seems probable that complete circulatory arrest can be safely withstood for at least 45 minutes. Most intracardiac procedures can be completed during this time.

There is no reason why cooling should not be carried still further. It is not unreasonable to suppose that, at a temperature lower than 10°C, it would be possible to carry out any type of cardiovascular surgery, however time-consuming, which may be visualised for the future.

It is natural for us to compare this method with that of cardiopulmonary bypass using a pump-oxygenator, of which we have had considerable experimental and some clinical experience. It would be premature at this stage to discuss the differences in detail. Some of the advantages

of using hypothermia in the manner described are obvious, others are more subtle.

Greater experience may confirm our growing belief that profound cooling with cardiac bypass will play an increasing part in the intracardiac surgery of the immediate future. This will be at the expense of cardiopulmonary bypass at normal temperatures, using a pump-oxygenator.

Summary

Three children with congenital intracardiac lesions have been operated upon using a new technique with cooling to 15°C. The first patient died from heart-block after partial correction of a persistent atrioventricular canal of the complete variety, which was virtually inoperable. After a period of total circulatory arrest of 46 minutes this infant appeared to be recovering.

The other two patients have survived. One had right atriotomy and ventriculotomy for obliteration of an atrial and ventricular septal defect. Repair of the latter necessitated resection of the medial cusp of the tricuspid valve and its resuture. In this patient the total circulatory arrest lasted 45 minutes.

The second surviving patient had a repair of a ventricular septal defect which required circulatory arrest for 25 minutes.

In no case did ventricular fibrillation occur. Hæmolysis was negligible and there were no significant biochemical upsets. The survivors show no evidence of neurological or other damage and have made uneventful recoveries.

Sir Clement Price Thomas has been a never-failing source of advice and encouragement.

Our thanks are also due to Miss Sarah Minter and Miss Pamela Brown, and Miss Joan Sherwood, theatre sisters and ward sister respectively, whose devoted help has contributed so much to this work.

Addendum

Since this paper was submitted for publication four additional patients have been operated upon for the correction of intracardiac defects. There was one death 24 hours after operation in an infant weighing 8 lb. This was probably due to heart-block. One of the three successes was a patient aged 49 years who had complete cardiac arrest for 42 minutes at 15°C.

THE CAUSE OF DIGITAL CLUBBING

TESTING A NEW HYPOTHESIS

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CLUBBED fingers differ from normal fingers in several respects. The difference in size and shape of the terminal phalanx and nail is obvious. There is interstitial œdema (Campbell 1924), and vascular engorgement with dilatation of the arterioles and venules (Chorr and Swenson 1946, Lovell 1950). The capillaries, however, are of normal size and capillary pulsation is not found (Rominger 1920, de Haas 1939, Lovell 1950). Although the blood-flow is increased (Mendlowitz 1938, Wilson 1952, Logan et al. 1954) the blood is thought to pass mainly through dilated arteriovenous (A.V.) anastomoses (Wilson 1952). This causes congestion of the venules with oxygenated blood under relatively high pressure, and produces local tissue hypertrophy, which is analogous to gigantism in a limb with a proximal A.V. fistula. The restriction of the hypertrophic changes to the fingers, toes, and occasionally the nose, is explained by the fact that these are the regions most richly endowed with A.V. anastomoses (Grant and Bland 1929).

The structural and functional changes in clubbed fingers are therefore quite well elucidated. But the way these changes are brought about in the diverse diseases complicated by clubbing is poorly understood. At present there are two main hypotheses:

(1) The occasional relief of the symptoms of hypertrophic pulmonary osteoarthropathy after vagotomy, noted by Pavlovsky (1947), Hansen (1952), Flavell (1956), and Huckstep and Bodkin (1958), suggests that the perverted circulation in the tips of the digits is mediated reflexly through the efferent nerves of the lung.

This explanation, however, seems untenable since, in the cases reported by these workers, there was no disappearance of the finger clubbing after vagotomy, and no explanation is offered for the clubbing sometimes found in congenital heart-disease and other non-pulmonary diseases.

(2) Clubbing is attributed to an endocrine imbalance, either primary, as in myxœdema acropachy (Thomas 1933), or secondary, as a result of pituitary involvement by carcinoma (Fried 1943, Bloom 1948, Freeman 1958).

This theory fails also to explain the clubbing of congenital heart-disease, and no details are offered as to what the endocrine imbalance actually is, how it is brought about by bronchogenic carcinoma, or how it manages to affect specifically the tips of the fingers and toes. The changes in the digits in acromegaly are quite distinct from those found in clubbing or hypertrophic pulmonary osteoarthropathy.

A case reported by Dorney et al. (1955), and the cases mentioned by Wood (1956), suggest a different possibility.

Dorney et al. describe a case without an aortic arch in which only the right arm and head received oxygenated blood from the left ventricle; the left arm and lower part of the body were supplied with mixed venous blood through a dilated pulmonary artery and patent ductus arteriosus. There was clubbing of the digits of the left hand and both feet, but not of the fingers of the right hand. Wood describes two cases of Eisenmenger's complex with a similar abnormality in that the lower limbs were fed by mixed venous blood through a patent ductus arteriosus; the toes were clubbed, but not the fingers.

From these observations it seems that if the fingers or toes are supplied with blood which has passed normally through the lungs no clubbing develops, whereas if the blood-supply is solely or partly venous clubbing is produced. This suggests that the lungs remove from mixed venous blood some substance which is capable of dilating A.V. anastomoses, and so stimulating the development of clubbing. In 1901, Béclère suggested the possibility of:

"une modification chimique du plasma dans lequel sont baignés les éléments anatomiques de la périphérie par suite de la retention plus prolongée qu'à l'état normal dans la plasma de toutes les substances destinées à être éliminées par les poumons, en particulier, de l'acide carbonique".

Although it is unlikely that failure of the lungs to remove carbon dioxide or to oxygenate fully the blood is responsible for clubbing (Cudkowicz and Wraith 1957) the notion of the lungs as a detoxicating organ of the venous blood arriving from the body deserves more attention. The lungs are probably capable of destroying serotonin (5-hydroxytryptamine) (Bradley et al. 1950). Many other vasoactive substances have been isolated from blood and tissues (Gaddum 1936). The compound which best fits the specification necessary for the production of clubbing —i.e., one which acts preferentially on the A.V. anas-

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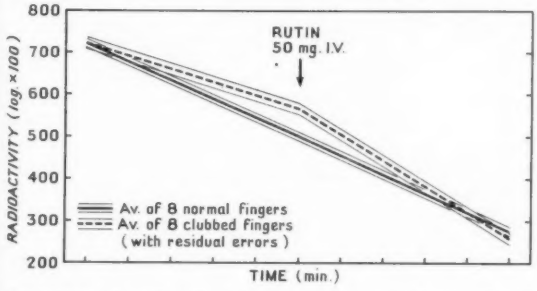
tomoses—is 'Vasodilator material' or reduced ferritin (Granick 1951, Shorr 1954). In very small quantities reduced ferritin is capable of inhibiting the vasoconstrictive action of circulating adrenaline on the musculature of the smaller arterioles. If reduced ferritin is oxidised in the presence of living tissue, it is inert when tested against adrenaline.

A new hypothesis to account for clubbing may be framed thus. In certain cases of lung-disease and cyanotic congenital heart-disease mixed venous blood is shunted past normal lung tissue. The reduced ferritin which it contains escapes oxidation and enters the systemic circulation in vasoactive form. It dilates the A.V. anastomoses by antagonising the vasoconstrictive action of circulating adrenaline, so producing the changes of digital clubbing. This hypothesis could best be tested by measuring the amount of reduced ferritin in arterial blood. This is extremely difficult to do. Reduced ferritin, however, is specifically antagonised by the flavonoid rutin (Crismon et al. 1950). If the hypothesis is correct, therefore, the circulatory changes in clubbed fingers should be counteracted by rutin, whereas the circulation in normal fingers will remain unaltered. The following experiment demonstrates this.

Materials and Methods

Eight subjects without clubbing and eight subjects with clubbing were studied.

Of the eight subjects with normal fingers, four were normal adult males; the others had an oatcell bronchogenic carcinoma,



Absorption of radiosodium from the dorsum of normal and clubbed fingers.

a large lung abscess of the right upper lobe, sarcoidosis of both lungs, and diffuse pulmonary fibrosis of unknown ætiology. The eight patients with clubbing had extensive fibrotic tuberculosis with bronchiectasis, Eisenmenger's complex with variable shunt (probably through the atrial septum), rheumatic heart-disease, congenital clubbing, bronchogenic carcinoma with multiple peripheral deposits, hidradenoma of the lung and pleura, pulmonary fibrosis with chronic bronchitis, and, in one case, recent clubbing of unknown cause (? early carcinoma of the lung). In all of them the clubbing was moderate or gross.

The circulation through the fingers was studied by measuring the clearance of subcutaneous radiosodium (Kety 1948).

Radiosodium (^{24}Na), as isotonic sodium chloride, was injected 2–3 mm. proximal to the nail fold of the ring or middle finger. In each case the finger was supported in a 'Plasticine' mould resting on the platform of a burette stand. The radioactive sodium chloride was diluted with ordinary isotonic saline so that, when 0·1 ml. of the mixture was placed in a Mantoux syringe $^1/_2$ in. away from a Geiger counter, about 1000 counts per sec. were recorded. This was then injected subcutaneously through a size 20 needle. A Geiger-Müller counter (GM 4 end-window tube) was supported above the finger by a clamp attached to the burette stand. The gamma radiation was recorded with a 'Burndept' rate-meter and transcribed graphically. The measured radioactivity declined in an exponential fashion as the radiosodium was absorbed into the bloodstream.

When about half the initial activity had disappeared, rutin 50 mg. (composition: rutin 50 mg., water 0·5 ml., phenylmercuric nitrate 0·1 mg., dimethyl acetamide to 5 ml.) in 10 ml. of normal saline was injected intravenously (taking about 20–30 sec.) into the opposite arm. Records of skin temperature were taken with a thermocouple.

TABLE I—RADIOSODIUM-ABSORPTION STUDIES IN SUBJECTS WITH NORMAL FINGERS

Subject	Slope of regression line		t
	Before rutin	After rutin	
Normal	−12·470	−11·378	1·227
,,	−10·632	−15·138	4·560
,,	−12·425	−17·091	4·380
,,	−18·660	−19·052	0·510
Carcinoma	−6·839	−9·522	4·640
Sarcoid	−10·275	−4·245	−10·400
Fibrosis of lung	−8·624	−10·090	2·270
Lung abscess	−8·621	−7·907	−1·469
Average	−11·068	−11·803	0·716*

* For 36 degrees of freedom.

Results

Values of radioactivity were read from the graph at $^1/_4$ min. intervals. Because the decline of activity was exponential (Kety 1948), the logarithms of the activity values were used. The relation between activity and time then becomes linear, and the slope of the line obtained on plotting this relationship is a measure of the rate of disappearance of the radiosodium. This rate is constant in the absence of disturbing factors (Garretts et al. 1958), and depends principally on the capillary flow in the region where the radiosodium has been injected. In each case the slope of the absorption-rate was calculated before and after the administration of rutin. The best estimates of slopes (regression coefficients) were calculated by the method of least squares (see figure). The t test of significance was applied to the difference between the slopes so calculated (tables I and II).

The slopes of the lines do not differ before and after the administration of rutin in normal fingers (average: before −11·068, after −11·803). This is confirmed by calculation of the t value for each pair of regression coefficients. The average t value is 0·716 ($n=40$), which shows there is no significant difference between the slopes ($P > 0·05$). In clubbed fingers there was a notable increase in the slope of absorption after rutin (average: before −7·977, after −15·115) and the average t value for the pairs of regression coefficients is 9·822, indicating a highly significant difference ($P < 0·001$). A further point of interest is that the rate of absorption of radiosodium from clubbed fingers is much slower than from normal fingers

TABLE II—RADIOSODIUM-ABSORPTION STUDIES IN SUBJECTS WITH CLUBBED FINGERS

Subject	Slope of regression line		t
	Before rutin	After rutin	
Tuberculosis and bronchiectasis	−7·424	−10·852	5·122
Eisenmenger's complex	−6·598	−9·585	4·529
Rheumatic heart-disease	−6·176	−10·830	6·528
Congenital clubbing	−7·738	−13·900	17·900
Carcinoma	−15·147	−31·440	16·790
? Carcinoma	−3·212	−9·518	9·413
Hidradenoma	−10·839	−14·636	5·647
Bronchiectasis	−7·686	−20·161	12·650
Average	−7·977	−15·115	9·822*

* For 36 degrees of freedom.

(−7·977 for clubbed fingers, compared with −11·068 for normal fingers). After rutin, however, the rate of absorption is relatively greater (−15·115 and −11·803).

In some clubbed fingers the rutin produced the appearance of capillary pulsation under the nails. There were no significant changes in skin temperature.

Discussion

Rutin, in an intravenous dose of about 0·5 mg. per kg. body-weight, has been shown to increase the absorption-rate of injected radiosodium from the subcutaneous tissues of clubbed fingers but not of normal fingers.

The rate of disappearance of radiosodium depends mainly on the total surface area of functioning capillaries in the area in which it is placed (Garretts et al. 1958). It seems therefore that rutin produces capillary dilatation in clubbed, but not in normal, fingers. The results suggest also that capillary flow is relatively diminished in clubbed fingers compared with normal fingers, and that rutin corrects this. The return of blood-flow to the capillary bed may be brought about by closure of the A.V. anastomoses, and this could possibly be effected by the antagonism of rutin to reduced ferritin in the circulation. The reduced ferritin itself may open the A.V. anastomoses by antagonising circulatory adrenaline.

From this experiment it may be deduced that the circulation in clubbed fingers is peculiar in that it is altered by rutin; and, because of the specific antagonism of rutin for ferritin, it may be suggested that reduced ferritin is responsible for the perverted circulation in the fingers.

The presence of reduced ferritin in the blood supplying clubbed digits may be explained by a shunt of mixed venous blood past the lung into the systemic circulation. In cyanotic congenital heart-disease and A.V. aneurysm of the lung the cause of a shunt is obvious, the shunt is copious, and the clubbing gross. In lung-disease associated with clubbing the mechanism of the shunt is less clear. Mixed venous blood in the pulmonary arteries supplying a diseased part may either escape passage through normal lung tissue or be deviated through pulmonary A.V. anastomoses. Some observations have been made favouring the latter possibility.

Ray and Fisher (1953) pointed out that clubbing is more commonly associated with carcinomas in the periphery of the lung than with those near the hilum; and tumours of the visceral pleura are particularly liable to produce gross clubbing. One possible explanation is that carcinomas near the hilum are supplied mainly by the bronchial arteries, and peripheral carcinomas by the pulmonary arteries. Perhaps more important, however, is the fact that pulmonary A.V. anastomoses are commonest in the cortex of the lung and immediately under the visceral pleura (Tobin and Zariquiez 1951, Morais et al. 1957). These A.V. shunts open under conditions of local irritation (Rahn et al. 1952), and possibly a local lesion may provoke their dilatation also. The relatively increased frequency of clubbing in peripheral lesions of the lungs would then be explained.

The effect of hilar pneumonectomy or vagotomy on the symptoms of pulmonary hypertrophic osteoarthropathy may result from interruption of local lung reflexes. Reflex dilatation of pulmonary A.V. anastomoses would cease and the shunt would close down. The immediate relief of pain so produced could then be explained by the cessation of the shunt of endogenous pain-producing substances into the systemic circulation.

We need not suppose that there is only one cause of clubbing. But the evidence outlined suggests that the clubbing associated with intrathoracic disease is produced by the shunting of a vasoactive substance past the lung, where it is normally destroyed. In view of the specific action of rutin in altering the circulation in clubbed fingers, this substance may possibly be reduced ferritin.

Clubbing associated with biliary cirrhosis (Parmentier and Castaigne 1901), sprue, ulcerative colitis, and other abdominal diseases has not been investigated by the technique described here. But the presence of ferritin in large quantities in the organs affected may be of ætiological importance. The clubbing associated with thyroid disease (Freeman 1958) may develop for entirely different reasons —perhaps a disparity between blood-supply and tissue needs, altered by hormones, is responsible. One patient with congenital clubbing, investigated in this series, was sensitive to rutin. This suggests an anomaly of the structure or function of the pulmonary circulation which has hitherto remained undetected.

As Bigler (1958) says, "there is an abundance of speculation concerning mechanisms of clubbing in previous publications" and this paper is no exception. Many aspects of the problem require further investigation. The musculature of the smallest arterioles and venules is now thought to be relatively independent of autonomic nervous control. It is more sensitive to the vasoactive substances arriving in the bloodstream or to those released locally. In keeping with this is the observation by Wilson (1952) that the increased blood-flow in clubbed fingers is unaffected by denervation. Apart from this, little is in fact known about the action and control of the A.V. anastomoses in the tips of the digits.

Likewise, the effect of disease on the pulmonary circulation is little understood. Cudkowicz and Wraith (1957) suggest that bronchopulmonary shunts develop constantly in the affected part of the lungs in patients with clubbing. These shunts are thought to exist because of the findings on injection studies, and because oxygenated blood can be withdrawn from branches of the pulmonary artery in the diseased lobes. But it is possible that the oxygenated blood comes through dilated pulmonary A.V. anastomoses rather than bronchopulmonary shunts. Moreover the operation most favouring the development of bronchopulmonary shunts—i.e., ligation of the pulmonary artery—has relieved clubbing (Wyburn-Mason 1948). Hence the ætiological importance of bronchopulmonary shunts in clubbing cannot be established.

Disorders of the peripheral circulation caused by endogenous vasoactive substances in abnormally large amounts are well known—e.g., the generalised pallor due to release of noradrenaline from a phæochromocytoma, or the flushing associated with carcinoid tumours. Digital clubbing may perhaps be the long-term result of an analogous phenomenon—namely, dilatation of A.V. anastomoses by reduced ferritin which has evaded destruction by lung tissue.

Summary

These radiosodium-absorption studies have shown that the capillary flow is less in clubbed fingers than in normal fingers. This difference can be counteracted by the intravenous administration of rutin.

Because rutin has a specific antagonism for reduced ferritin, the abnormal digital circulation associated with clubbing is thought to be due to the presence of reduced ferritin.

The hypothesis is postulated that the common feature of intrathoracic diseases, which induce clubbing, is the presence of pulmonary arteriovenous shunts, or an equivalent shunt of mixed venous blood into the systemic

circulation. Reduced ferritin passes through these shunts instead of being rendered inert by oxidation in normal lung tissue.

My thanks are due to Dr. M. G. Garretts, who introduced me to the radiosodium technique; to numerous colleagues who have encouraged me in this work, especially Dr. K. F. R. Schiller and Dr. Christine Tyler; and to the patients and students who submitted to these studies. The paper was prepared with the assistance and forbearance of my chiefs, Dr. Howard Nicholson and Dr. Peter Heaf, and I am indebted to Dr. E. E. Pochin and Dr. E. A. Blake Pritchard, for permission to study cases under their care.

REFERENCES

Béclère, M. A. (1901) *Bull. Soc. méd. Hôp. Paris*, **18**, 283.
Bigler, F. C. (1958) *Amer. J. Path.* **34**, 237.
Bloom, W. (1948) *Ann. intern. Med.* **29**, 361.
Bradley, T. R., Butterworth, R. F., Reid, G., Trautner, E. M. (1950) *Nature, Lond.* **166**, 911.
Campbell, D. (1924) *Brit. med. J.* i, 145.
Chorr, R., Swenson, P. C. (1946) *Amer. J. Rœntgenol.* **55**, 325.
Crismon, J. M., Berez, R. R., Madden, J. D., Fuhfman, F. A. (1950) *Amer. J. Physiol.* **164**, 391.
Cudkowicz, L., Wraith, D. G. (1957) *Brit. J. Tuberc.* **51**, 14.
de Haas, W. H. D. (1939) *Ned. Tijdschr. Geneesk.* **83**, 384.
Dorney, E. R., Fowler, N. O., Mannix, E. P. (1955) *Amer. J. Med.* **18**, 150.
Flavell, G. (1956) *Lancet*, i, 260.
Freeman, A. G. (1958) *ibid.* ii, 57.
Fried, B. M. (1943) *Arch. intern. Med.* **72**, 565.
Gaddum, J. H. (1936) Gefasserweiternde Stoffe der Gewebe. Leipzig.
Garretts, M., Jarrett, A., Osborn, S. B. (1958) *Brit. J. Derm.* **70**, 22.
Granick, S. (1951) *Physiol. Rev.* **31**, 500.
Grant, R. T., Bland, E. F. (1929) *Heart*, **15**, 385.
Hansen, J. L. (1952) *Acta med. scand.* **142** (suppl. 266), 467.
Huckstep, R. L., Bodkin, P. E. (1958) *Lancet*, ii, 343.
Kety, S. S. (1948) *Amer. J. med. Sci.* **215**, 352.
Logan, J. S., Marshall, R. J., Shepherd, J. T., Whelan, R. F. (1954) *Irish J. med. Sci.* **339**, 127.
Lovell, R. R. (1950) *Clin. Sci.* **9**, 299.
Mendlowitz, M. (1938) *ibid.* **3**, 387.
Morais, B. J., Cruz, M. J., de Souza, A. (1957) *Brit. J. Tuberc.* **51**, 223.
Parmentier & Castaigne (1901) *Bull. Soc. méd. Hôp. Paris*, **18**, 275.
Pavlovsky, A. J. (1947) *Bol. Acad. argent. Cirug.* **31**, 857.
Rahn, H., Stroud, R. C., Tobin, C. E. (1952) *Proc. Soc. exp. Biol., N.Y.* **80**, 239.
Ray, E. S., Fisher, H. P. (1953) *Ann. intern. Med.* **38**, 239.
Rominger (1920) *Dtsch. med. Wschr.* **46**, 158.
Shorr, E. (1954) *Harvey Lect.* **50**, 112.
Thomas, H. M., Jr. (1933) *Arch. intern Med.* **51**, 571.
Tobin, C. E., Zariquiez, M. O. (1951) *Proc. Soc. exp. Biol., N.Y.* **75**, 827.
Wilson, G. M. (1952) *Quart. J. Med.* **21**, 201.
Wood, P. (1956) Diseases of the Heart and Circulation; p. 396. London.
Wyburn-Mason, R. (1948) *Lancet*, i, 203.

OXYTOCIN AND RENAL CORTICAL NECROSIS

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IT has recently been shown that in the œstrous phase of the sex cycle or after treatment with ovarian hormones the rat responds to oxytocin by vasoconstriction and a rise in blood-pressure (Lloyd 1958, Pickford 1958). This unexpected observation is important to the physiologist because oxytocin has not hitherto been suspected of having significant vasoconstrictor activity and to the clinician because it raises the question whether oxytocin may be implicated in any of the vascular complications of late pregnancy in which vasoconstriction is recognised or suspected. One of these complications—namely, renal cortical necrosis—lends itself readily to experimental study, and in the present paper we describe how the essential features of this condition can be produced by the subcutaneous injection of oxytocin into rats suitably "sensitised" by ovarian hormones. It must be emphasised that a very large dose of oxytocin is necessary.

The Experiment

Freshly weaned female albino rats were ovariectomised and then divided into two groups. The animals in the first group were treated with large doses of œstrogens, either as subcutaneous implants of œstradiol (10 mg.) or as daily injections of up to 0·25 mg. œstradiol benzoate in oil. These rats were also given several daily doses of up to 1 mg. of progesterone in oil, because œstrogens alone will not cause sensitisation in the spayed rat (Lloyd 1958). The animals in the second group served as unsensitised controls.

After ten or more days of this preliminary treatment a single subcutaneous injection of synthetic oxytocin ('Syntocinon', Sandoz) or natural oxytocin ('Pitocin', Parke, Davis) was given in a constant volume of physiological saline solution (5 ml. per 100 g. body-weight). The injection was given through shaved skin, and the puncture mark was sealed with adhesive tape. Most preparations of oxytocin contain 0·5% chlorbutol ('Chloretone') as a preservative. This substance is a hypnotic, and in early experiments caused deep or fatal coma whenever large volumes of the hormone were given to small animals. It was therefore found necessary to remove the chlorbutol.

This can be done by continuous ether extraction at pH 3·8–4·0 for forty-eight hours; but a more convenient method, based on the volatility of chlorbutol, is to adjust the pH to 3·8–4·0 and evaporate to one-fifth volume in a rapid stream of nitrogen at 50°C.

The rats were killed twenty-four hours after the injection of oxytocin and the kidneys were examined histologically. In other experiments the effect of intravenous injections of oxytocin on the appearance of the living kidney was studied. When intravenous injections were given the volume of each injection was limited to 0·1 ml. per 100 g. body-weight.

Results

In living rats sensitised in the manner described above, observation of the kidney at laparotomy leaves no doubt that synthetic oxytocin can cause gross cortical ischæmia. A few seconds after an intravenous injection of 20<30 milliunits multiple areas of intense greenish pallor appear on the surface of the kidney, enlarge, coalesce to involve the whole surface except for a small zone near the hilum, and then gradually recede. The ischæmia which follows a single intravenous injection is relatively short-lived; and, in order to cause structural damage in sensitised rats, oxytocin must be given subcutaneously in much larger doses—i.e., from 4 to 20 or more units per 100 g. body-weight (30 experiments). At the lower level of this dose scale the only histological abnormality is a thin, cloudy eosinophil exudate in the lumen of Bowman's capsule and the tubules. At the upper end of the scale the greater part of the cortex is converted into multiple anæmic infarcts, usually with hæmorrhagic borders (figs. 1 and 2). In the infarcts the tubule cells are completely necrosed and devoid of nuclei. Some glomeruli may escape damage, others may be completely necrosed and many are often so deeply injected as to be clearly visible through the capsule of the kidney in life. The medulla remains substantially free from necrosis, but patchy tubular dilatation is com-

Fig. 1—Kidney of a young rat treated with ovarian hormones followed by a large subcutaneous dose (30 units) of synthetic oxytocin, showing (1) large pale areas of cortical necrosis and (2) deeply congested (black) glomeruli (×7).

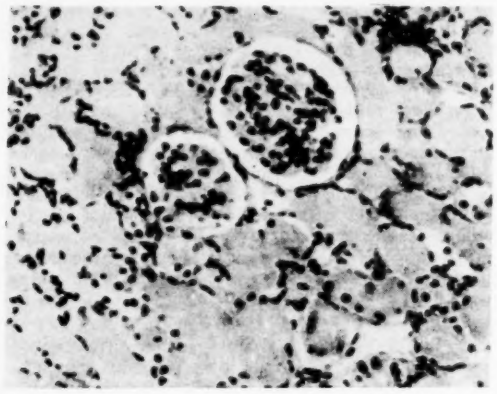

Fig. 2—Kidney of young rat similarly treated, showing completely necrosed tubules surrounding relatively normal glomeruli (×120).

mon. The renal arteries mostly appear normal, but a few examples of circumscribed medial necrosis of large arteries have been observed. The effects of natural oxytocin are essentially similar (23 experiments).

In unsensitised spayed control rats (18 experiments) commercial preparations of synthetic or natural oxytocin containing 10 units per ml. caused no blanching of the kidney on intravenous injection (0·1 ml.), while subcutaneous injection of as much as 100 units caused neither naked-eye nor microscopic damage in the kidney. Even in the absence of ovarian hormone, however, the renal arterial muscle is not entirely non-reactive to oxytocin. A specially concentrated solution of synthetic oxytocin containing 70 units per ml. caused gross blanching of the kidney on intravenous injection (0·1 ml.). Thus the effect of ovarian hormones on the reactivity of vascular muscle to oxytocin is not a qualitative but a very large quantitative change.

Comment

In attempting to assess the above findings it is necessary first to relate them to certain earlier observations. It has been shown (Byrom 1937) that identical necrotic changes in the kidney can be caused in normal rats by subcutaneous injection of vasopressin. These changes were shown to be direct results of ischæmia, and moreover can be increased tenfold or more by prior treatment with œstrogens (Byrom 1938). The *relative* effects of the two neurohypophyseal hormones on vascular muscle, measured by renal damage, may be summed up in two statements: (1) that at any given state of ovarian activity vasopressin is usually a better vasoconstrictor than oxytocin; and (2) that oxytocin is a better vasoconstrictor in the presence of ovarian activity than vasopressin is in its absence. Thus in sensitised spayed rats definite necrosis may be caused by a threshold dose of about 0·5 units of vasopressin or about 5 units of oxytocin. In the unsensitised rat a *single* dose of vasopressin, however large, rarely caused more than degenerative changes short of necrosis, while oxytocin caused no definite damage.

To these quantitative differences an apparently qualitative one must be added. Progesterone as well as œstrogen is necessary for the sensitisation of vessels to oxytocin, whereas in the case of vasopressin œstrogen alone is effective, although progesterone increases the sensitisation.

So far two instances of œstrogen-sensitisation of plain muscle to neurohypophyseal hormones have been mentioned. There remains a third and better-known instance —namely, the fact that the reactivity of the uterine muscle to oxytocin is augmented by œstrogens (Bourne and Burn 1928). Here again the role of progesterone is different, for it directly opposes the sensitising effect of œstrogens (Knaus 1929). The three phenomena are presumably related in some way, but no explanation can be attempted as long as the mode of action of the pituitary and ovarian hormones remains unknown.

Clinical Considerations

In man renal cortical necrosis usually follows concealed accidental hæmorrhage in the last third of pregnancy (Sheehan and Moore 1952), often in pre-eclamptic patients. In fatal cases most of the cortex of the kidney is replaced by confluent areas of necrosis. These have all the characters of anæmic arterial infarcts, but, except in the later stages, when secondary thrombosis may occur, the larger arteries are free from obstruction. It therefore seems that the renal damage results from sudden severe cortical ischæmia due to simple arterial spasm and/or diversion of blood from the cortex to the medulla (Trueta et al. 1947).

The cause of this presumed functional ischæmia is quite unknown. From time to time suspicion has fallen on various vasoconstrictor agents, but so far none has been incriminated by direct evidence. As a newly revealed vasoconstrictor oxytocin must clearly be added to the list of suspects. Ovarian hormones and oxytocin are intimately concerned in pregnancy and parturition, and the present results show that, when toxic doses of oxytocin are given to rats sensitised with ovarian hormones, the kidney is particularly vulnerable and, as in the case of vasopressin, presents all the features of cortical necrosis in man. There are two good reasons for resisting the inference that the latter is caused by oxytocin. In the first place the toxic dose of oxytocin in the rat far exceeds what may reasonably be expected of natural secretion. Secondly, although the reactivity of the uterine muscle to oxytocin may be increased several hundredfold at full term, there is no direct evidence that vascular muscle is sensitised in normal or abnormal human pregnancy. The problem must therefore be passed to the obstetrician for further study. Observations on normal and toxæmic patients before, during, and after continuous intravenous injections of oxytocin would seem a useful first step. We suspect that the volume of urine may be a more sensitive indicator of vascular sensitisation than the systemic blood-pressure.

Summary

Intense renal ischæmia leading to massive cortical necrosis can be provoked in the ovariectomised rat by preliminary treatment with ovarian hormones followed by a large subcutaneous dose of synthetic or natural oxytocin.

This observation is a logical corollary of the demonstration by Lloyd (1958) that oxytocin assumes vasoconstrictor properties in the presence of ovarian activity.

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REFERENCES

Bourne, A. W., Burn, J. H. (1928) *Lancet*, ii, 1020.
Byrom, F. B. (1937) *J. Path. Bact.* **45**, 1.
— (1938) *Lancet*, i, 129.
Knaus, H. (1929) *Arch. Gynaek.* **138**, 201.
Lloyd, S. M. (1958) *J. Physiol.* **141**, 37 P.
Pickford, L. M. (1958) Personal communication.
Sheehan, H. L., Moore, H. C. (1952) Renal Cortical Necrosis and the Kidney of Concealed Accidental Hæmorrhage. Oxford.
Trueta, J., Barclay, A. E., Franklin, K. J., Daniel, P. M., Prichard, M. M. L. (1947) Studies of the Renal Circulation. Oxford.

TREATMENT OF TETANUS WITH CHLORPROMAZINE AND BARBITURATES

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THIS paper records the results of a clinical trial on 96 patients with tetanus in which chlorpromazine was compared with a combination of chlorpromazine and barbiturates in 56 non-neonatal cases, and with a combination of barbiturates (for the first twenty-four hours only) and chloral hydrate in 40 neonates. The results of treatment in 57 subsequent cases of tetanus neonatorum are also briefly reported.

In a previous trial we allotted 75 patients at random to two treatment groups, using either chlorpromazine or barbiturates to control reflex spasms (Laurence et al. 1958). We showed that there was no significant difference in the outcome between the two groups, but we found chlorpromazine easier to manage. Because large doses of both drugs were sometimes required to control spasms and toxic effects were encountered, we limited the doses of the drugs used in our second trial and made use of the potentiating effect of chlorpromazine on barbiturates. The design of this second trial was the same as that of the first, and feeding, nursing procedures, and treatment with anti-tetanus serum and with prophylactic penicillin were similarly standardised, but different drug dosages and combinations were used.

Drugs Used to Control Spasms

Non-neonatal Patients

Such patients in the chlorpromazine group received 100 mg. intramuscularly on admission, with subsequent four-hourly doses of 100–200 mg. according to the severity, a limit of 1000 mg. being set for any twenty-four-hour period. Smaller doses were used for those under 10 years of age. Only 3 patients needed more than 600 mg. in any one day, and control of spasms was not difficult.

Every patient in the group treated with the combination of chlorpromazine and barbiturates was given 50 mg. chlorpromazine and 200 mg. phenobarbitone intramuscularly on admission. Thereafter chlorpromazine dosage was fixed at 50 mg. four-hourly, additional sedation being achieved with phenobarbitone sodium as required. Control was usually good and easily effected by this combination, although the daily maximum of 300 mg. chlorpromazine was exceeded in 1 case. Only 3 patients required more than 1·0 g. phenobarbitone sodium in addition to 300 mg. chlorpromazine in any one day.

Occasionally sedation was required urgently. For this purpose in the chlorpromazine group 100 mg. was given intravenously, while intramuscular or intravenous amylobarbitone sodium 0·25–1·0 g. was used in the group treated with the combination of chlorpromazine and phenobarbitone.

Neonatal Patients

Neonates treated with chlorpromazine were given 25 mg. intramuscularly on admission, and thereafter the same dose not more frequently than four-hourly. Control of spasms was often poor on the maximum daily dose of 150 mg. 1 infant needed as much as 200 mg. chlorpromazine, and another 60 mg. phenobarbitone sodium in addition to 150 mg. chlorpromazine to control the spasms.

Those in the barbiturate-chloral group were treated in the first twenty-four hours only with phenobarbitone sodium in 60 mg. doses intramuscularly, up to a maximum of five doses, the aim being to achieve sedation rapidly to facilitate the passage of a stomach-tube. After that no further phenobarbitone was given and control was maintained with chloral hydrate in 120 mg. doses given not more frequently than four-hourly by the stomach-tube left in situ. Spasms were poorly controlled in 4 patients, of whom 3 needed additional sedation with phenobarbitone in the first twenty-four hours, and the 4th 50 mg. chlorpromazine to facilitate the passing of the stomach-tube.

TABLE I—COMPARISON OF GROUPS

—	Non-neonates		Neonates	
	Chlorpromazine	Chlorpromazine/barbiturate combination	Chlorpromazine	Barbiturate/chloral-hydrate combination
No. of cases	29	27	20	20
Average age	13 yr.	21 yr.	5·7 days	7·7 days
Severity:				
Severe	24	16	20	19
Moderate	4	7	0	1
Mild	1	4	0	0
Site of wound:			All umbilicus	
Leg	16	7		
Arm	0	3		
Trunk	1	0		
Head	1	2		
Uterus	1	3		
Multiple	5	3		
No wound	5	9		
Av. incubation period (days)	13	11	5·2	6·8
Av. period of onset (hr.)	36	65	6·8	6·8
Deaths:				
Among all cases	15 (52%)	9 (33%)	19 (95%)	18 (90%)
Among severe cases	15 (63%)	8 (50%)	19 (95%)	18 (95%)

Results

As regards severity, our cases were classified as before—"mild" when there was rigidity but no reflex spasms, "moderate" when there were reflex spasms which were either mild or infrequent, and "severe" when frequent severe reflex spasms were present. The main points of difference between cases of tetanus are found in the incubation period, the period of onset of reflex spasms, the age of the patient, and the site of the wound. All of these factors affect the outcome of treatment, and we have listed them in table I, in which the groups are compared.

Analysis of the results in non-neonatal patients shows no statistically significant difference in the outcome between treatment with chlorpromazine and with the mixture of chlorpromazine and barbiturates (overall mortality-rates 52% and 33%, and mortality-rates among severe cases 63% and 50% respectively), and there are no significant differences betwen the two neonatal treatment groups (overall mortality-rates 95% and 90%, mortality-rates among severe cases 95% and 95%).

Causes of Death

In the non-neonatal series there was clinical evidence of respiratory embarrassment other than that due to pneumonia in 12 patients (21%), 10 of whom died. 5 patients had laryngeal spasms, 3 in the chlorpromazine

TABLE II—SUMMARY OF PULMONARY COMPLICATIONS (NECROPSY MATERIAL)

	Non-neonates		Neonates	
	Chlor-promazine	Chlor-promazine/barbiturate combination	Chlor-promazine	Barbiturate/chloral-hydrate combination
No. examined ..	16	9	17	17
Bronchopneumonia	4	3	4	6
Purulent bronchitis ..	1	1	..	..
Collapse	3	..	5	3
Ulcer of trachea with obstruction ..	..	..	..	1

group. Prompt administration of intravenous chlorpromazine was effective in all 5, but 3 died later. Other evidence of respiratory embarrassment was observed in 8 patients, none of whom survived; 4 were in each treatment group, and 1 had previously had laryngeal spasms. In 4 patients severe or continuous spasms were followed by gasping respiration or by apnœa without definite evidence of laryngeal spasms. There was respiratory obstruction on two successive days in another patient owing to the tongue falling back, and for this reason tracheotomy was performed—the only instance in the whole series. This patient subsequently died after a period of continuous spasms and shallow breathing. In the remaining 3 patients there were either irregular gasping respirations or abrupt cessation of breathing which did not follow repeated spasms.

Evidence of respiratory embarrassment was observed in 13 neonates (33%), all of whom died. Most often there was irregular gasping, and the infants were commonly cold and flaccid as well. Cyanotic attacks also occurred following apnœa rather than laryngeal spasms. Overdosage cannot be excluded as a cause of death in these neonates, but we think it more likely that in the majority death was due to tetanus intoxication of the medullary centres.

Contusion of the brain under a fracture may have contributed to death in 1 of the non-neonatal patients; but at necropsy the main complications were observed in the lungs, as in other series of cases of tetanus. Analysis of the incidence of such complications in the four treatment groups shows no striking differences (see table II). Bronchopneumonia was present in approximately a quarter of the patients given chlorpromazine alone, and in a third of all those treated with the combinations used. Collapse of the lung, usually patchy in distribution and seldom extensive, was more often observed in the chlorpromazine-treated groups. After recovering from tetanus, 1 of the neonatal patients died on the thirty-fifth day from respiratory obstruction caused by prolonged œsophageal intubation which resulted in ulceration of œsophagus into trachea. In at least half of the non-neonatal cases no cause of death was apparent at necropsy, and there was also no apparent cause in nearly half of the neonates.

Discussion

Although the mortality-rate among severe cases of tetanus remains considerable, adequate control of spasms in non-neonatal patients can be achieved with chlorpromazine alone or with a combination of this drug with phenobarbitone sodium in the dosages we have employed. Management is relatively easy, consciousness is not lost, and patients usually remain cooperative. Two-thirds of our patients in both treatment groups were satisfactorily fed by mouth. When a stomach-tube has to be passed or special procedures are necessary, chlorpromazine is a most useful relaxant; and we found it effective in the treatment of laryngeal spasms. Although the mortality-rates were similar whether we used chlorpromazine alone or in combination with barbiturates, we prefer the combination of the two drugs because control of spasms is readily achieved while the toxic effects of either drug used alone are avoided.

In animal experiments it has been found that there is a maximal dose above which anti-tetanus activity is not increased, and indeed the tetanus may be increased at very high doses (Laurence and Webster unpublished). From these experiments it would be expected that in man this critical dose is 200–300 mg. for non-neonates, but it is not possible to suggest a dose for neonates as there is no valid basis for comparison. If chlorpromazine is given more frequently than every two hours, tachyphylaxis (diminishing response to doses repeated at very short intervals) may occur (Laurence and Webster unpublished). This risk of losing therapeutic effect can be avoided by alternating chlorpromazine with phenobarbitone when the severity of the spasm calls for additional sedation.

Prognosis in tetanus seems to be most closely related to the period of onset of reflex spasms (Cole 1940). It is particularly bad when the period of onset is under forty-eight hours, as analysis of our material shows (Adams 1958). This period was very short in our neonatal cases (mean 6·8 hours), and it is not surprising that the mortality-rate was so high. Although control of spasms was poorly achieved among neonates in the trial reported here, and we accept the view that such control is one of the aims of treatment, we are doubtful whether control of spasms alone will save the majority of cases of tetanus neonatorum; for we believe that tetanus intoxication of the medullary centres is probably the most important factor determining the high mortality-rate.

We have subsequently treated 57 consecutive cases of tetanus neonatorum using similar standardised treatment but attempting to control spasms by other methods. 13 of these patients recovered. The average period of onset for this series (10·5 hours) was somewhat longer than in the trial reported above, and the overall mortality-rate (77%) was correspondingly lower. 13 of the most severe cases were selected for preliminary testing of tracheotomy (4 cases) and acetylpromazine, either alone or in combination with sodium phenobarbitone (9 cases); but all 13 died. Given intramuscularly not more frequently than four-hourly in 10 mg. doses, acetylpromazine did not appear to be any better than chlorpromazine. Acetylpromazine was tried because it has been shown to have ten times the activity of chlorpromazine against experimental tetanus (Laurence and Webster 1958). We treated the remaining 44 patients with a combination of chlorpromazine and barbiturate. We usually gave 100 mg. chlorpromazine and 120 mg. sodium phenobarbitone intramuscularly in divided doses over the first twenty-four hours, attempting to control spasms thereafter with half these amounts. All 13 patients who survived were in this group. Because there was selection, we cannot make valid comparisons with the results of our previous trials, but we believe that this combination has some merit for the control of spasms in tetanus neonatorum as it has in non-neonatal cases. We are accordingly using these drugs to control spasms in all cases in a further trial in which we are attempting to assess the role of tracheotomy in this disease.

Summary

A clinical trial on 96 tetanus patients allotted at random to two treatment groups practised concurrently is reported.

Chlorpromazine was compared with a combination of chlorpromazine and barbiturates in 56 non-neonatal cases, and with a combination of barbiturates (for the first twenty-four hours only) and chloral hydrate in 40 neonates; but in neither group were there statistically significant differences.

The results of treatment in a further 57 cases of tetanus neonatorum are recorded. For 44 of these, a combination of chlorpromazine and barbiturates was used, and 13 very severe cases were subjected to preliminary trials of acetylpromazine and tracheotomy.

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REFERENCES

Adams, E. B. (1958) *Proc. R. Soc. Med.* **51**, 1002,
Cole, L. (1940) *Lancet*, i, 164.
Laurence, D. R. (1958) *Proc. R. Soc. Med.* **51**, 1000,
— Berman, E., Scragg, J. N., Adams, E. B. (1958) *Lancet*, i, 987.
— Webster, R. A. (1958) *Brit. J. Pharmacol.* **13**, 334.

LIVER GLUTAMIC-ASPARTIC TRANSAMINASE ACTIVITY IN DIABETES

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THE transaminases catalyse important reactions in the interconversion of aminoacids and carbohydrate intermediates. The activity of these enzymes may therefore affect the rate of gluconeogenesis in the liver. Cortisone is generally believed to increase gluconeogenesis by the liver.

Brin and McKee (1956) and Gavosto et al. (1957) have shown that administration of this hormone to rats resulted in a distinct increase in liver-transaminase activity. Rosen et al. (1958) have similarly shown that hydrocortisone increased liver-transaminase activity of rats, and they suggest that these compounds exert their gluconeogenetic activity by virtue of their effect on liver-transaminase. Borel et al. (1957) have demonstrated an increased activity of liver-transaminase in rats fed on an exclusive meat diet; and Brin and McKee (1956) have shown an increase in activity as a result of fasting. The latter effect has been confirmed (Patrick 1958), but it was noted that although a 24-hour fast produced about a 10% increase in the *concentration* of liver-transaminase in the rat, the livers decreased in weight with fasting to such an extent that the total content of transaminase was decreased by about 15%. Nevertheless it seems clear that various conditions (glycocorticoid administration, high-protein diet, starvation) which are associated with increased liver gluconeogenesis are accompanied by an increase in transaminase activity per mg. of liver nitrogen. To this list of conditions may be added alloxan diabetes inasmuch as Copenhaver et al. (1951) and Rossi and Tomatis (1957) have also demonstrated a distinct increase in liver-transaminase activity in alloxan-diabetic rats. On the other hand, Beaton and Curry (1956) have demonstrated a slight increase in rat-liver transaminase as a result of repeated insulin administration. Donato (1957) found the serum-transaminase activity of six diabetic patients to be in the normal range. Bornstein (1957) has demonstrated inhibition of alanine-transaminase by two sulphonyl urea compounds, and has suggested that these compounds exert their hypoglycæmic effect by inhibiting transamination in vivo.

In view of the possible relation of gluconeogenesis to liver-transaminase activity it was considered of interest to study this enzyme in human liver from diabetic patients before and after treatment.

Biochemical Methods

The methods of obtaining the liver biopsy specimens, preparing the liver homogenates, and determining the nitrogen content have been described previously (Patrick and Tulloch 1957). The transaminase assay was carried out by a modification of the method of Karmen (1955), which depends upon spectrophotometric measurement of the oxidation of reduced diphosphopyridine nucleotide (D.P.N.H.), by oxaloacetate, which is a product of the transamination reaction. The volume of the assay system was 0·20 ml. and the final concentrations of the reagents were:

Liver 0·01–0·05 mg. per ml.	
Phosphate buffer pH 7·4	0·075*M*
Aspartate	0·040*M*
α-ketoglutarate	0·008*M*
Malic dehydrogenase (Sigma)	100 units per ml.
D.P.N.H. (California Biochemicals Ltd.)	0·07 mg. per ml.

Various control experiments were carried out to test the validity of this assay system as applied to human liver. It was found that oxidation of the D.P.N.H. was negligible after the first few minutes when either the aspartate or α-ketoglutarate was omitted. Thus, it is apparent that any substrates or oxidative enzymes present in the liver were diluted to such an extent as to render unimportant the side-reactions they might produce. Doubling or halving the concentration of the malic dehydrogenase or the concentration of D.P.N.H. had no effect on the rate of oxidation of D.P.N.H. From this it appears that the rate of oxidation of D.P.N.H. was limited by the production of oxaloacetate by the transaminase reaction. Addition of pyridoxal phosphate or of potassium cyanide to the human liver homogenates had no effect on the rate of oxidation of the D.P.N.H. in the assay system. This indicates that decreases observed in the activity in the enzyme in human liver resulted from decrease in the concentration of the enzyme protein rather than deficiency of the coenzyme, pyridoxal phosphate. Freezing the liver had no significant effect on the transaminase activity, and an aqueous liver homogenate retained full activity for at least 10 hours. The assays were carried out at room temperature which varied from 25° to 30°C. Experiments with human liver indicated that increase of temperature from 25° to 30°C increased the transaminase activity by about 30%. Accordingly the temperature was recorded for each assay, and a correction factor was applied so that each result could be expressed as activity at 25°C. Routinely, two dilutions of each liver homogenate were made—one at half the concentration of the other—and each enzyme dilution was assayed separately. The results of the two assays were generally in agreement to within 5%, and were averaged in the final result.

Clinical Material

19 patients (9 males and 10 females) with diabetes mellitus were studied; their ages ranged from 16 to 67 years. There was one classical type-I case, 3 J-type cases (Hugh-Jones 1955) and 15 type-II cases (Bornstein and Lawrence 1951). The type-I patient was a 16-year-old boy who had been diabetic for 4 months. He had been under treatment until 2 weeks before admission to hospital when his supply of insulin ran out. The 3 J-type cases were aged 16, 22, and 23 years and had been diabetic for 6 months, 4 years, and 6 months respectively. At the time of their admission to hospital 2 were stabilised on 160 and 190 units of insulin zinc suspension (lente), and the 3rd was previously untreated. The type-II cases were aged 38–67 years, and the duration of their diabetes was from

TRANSAMINASE ACTIVITY OF LIVER TISSUE OBTAINED AT BIOPSY IN DIABETIC PATIENTS

Urine at second biopsy	Case no.	Age (yr.)	Diabetic type	Duration of diabetes (yr.)	Fasting blood-sugar (mg. per 100 ml.)		Transaminase activity †	
					First biopsy	Second biopsy	First biopsy	Second biopsy
Free of sugar for 24 or 48 hr.	1	16	I	4/12	343	149	0·253	0·167
	2	23	J	4	405	133	0·192	0·126
	3	41	II	2	380	79	0·213	0·216
	4	38	II	1	226	125	0·139	0·123
	5	49	II	1	252	70	0·207	0·182
	6	59	II	7	362	162	0·274	0·125
	7	55	II	3/12	270	82	0·182	0·095
	8	57	II	2	263	31	0·232	0·121
	9	67	II	4/12	217	168	0·136	0·168
	10*	44	II	11/12	246	245	0·244	0·168
Free of sugar for several days	11	16	J	6/12	593	—	0·224	0·104
	12	50	II	5/12	315	78	0·164	0·090
	13	54	II	6	292	98	0·279	0·224
	14	66	II	7/12	266	39	0·220	0·107
	15*	60	II	2	274	150	0·239	0·167
Not free of sugar	16	22	J	6/12	272	140	0·248	0·262
	17	56	II	5	320	137	0·216	0·144
	18	38	II	3	293	138	0·199	0·115
	19*	54	II	9	242	225	0·208	0·200

* Treated by diet alone. † For units see text.

Case 10 received fructose as her sole source of carbohydrate. and possibly the fasting blood-sugar at the time of the second biopsy contained a small amount of fructose. Her urine had become and remained free of sugar. There was a subsequent fall in the fasting blood-sugar as glucose was reintroduced in place of fructose.

3 months to 9 years. Apart from 3 patients who were treated with diet alone, all patients were treated with diet plus insulin.

A liver biopsy was carried out before starting therapy and was repeated in the majority after the diabetic state had been stabilised. In 10 patients—1 type-I case, 1 J-type case, and 8 type-II cases—the repeat liver puncture was performed immediately the patient's urine became sugar-free. In 1 J-type and 4 type-II cases, including 1 treated by diet alone, the biopsy was not repeated until several days after the urine became sugar-free. In 4 cases (3 type-II and 1 J-type) the second biopsy was obtained before the patient's urine was sugar-free. 1 patient treated by diet alone discharged herself against advice, and the repeat biopsy was therefore obtained while she was still showing sugar in her urine. Apart from the patients stabilised on diet alone, all patients had diabetes of moderate severity.

The blood-sugar levels, done in the fasting state before therapy was started, ranged from 217 to 593 mg. per 100 ml., the majority being in the range 200–300 mg. per 100 ml. (see table). Liver-function tests were carried out on all but 3 of the cases; and these were within normal limits, except for 1 case with a moderately low plasma albumin-level of 2·9 g. per 100 ml. 5 patients (4 type-II, 1 J-type) had peripheral neuritis and 2 had cataract, but there was no other serious complication.

Results

The results, set out in the table, are expressed as millimoles of aminoacid transaminated per hour per mg. of liver nitrogen.

It is apparent that, despite wide variation in the transaminase activities from case to case, there is very generally a decrease in the transaminase activity after stabilisation of the diabetes. Considering only those cases with sugar-free urine at the time of the second biopsy, the average initial transaminase activity was $0{\cdot}213 \pm 0{\cdot}011$ units, and after treatment it was $0{\cdot}146 \pm 0{\cdot}012$ units. This decrease is highly significant statistically ($P = 0{\cdot}001$).

Discussion

The results indicate that in most cases the transaminase activity of the liver-cell is reduced by treatment of the diabetic state regardless of the type of diabetes and of the treatment given. There are exceptions to this, however, as 3 patients showed a greater transaminase activity at the time of the second biopsy. 1 of these patients (case 16) was still showing a little sugar in the urine at that time.

It is likely that the rate of gluconeogenesis varies from one case to the next. If gluconeogenesis is related to transaminase activity, a comparatively wide variation of the latter might be expected. There was no obvious relation between the initial transaminase activity and the type or duration of the diabetes, the weight of the patient, or the fasting blood-sugar level.

The change in transaminase activity following treatment of the diabetes did not appear to be related to the fall in the fasting blood-sugar level, the type of diabetes, the duration or type of treatment, or the insulin requirement. That the reduction in activity is not due solely to insulin administration is shown by the fact that 2 type-II patients (cases 10 and 15) who were treated by diet alone showed a considerable fall in activity. 1 other patient who was treated by diet alone (case 19) discharged herself before there was any appreciable improvement in her diabetic state (fasting blood-sugar 242 and 245 mg. per 100 ml.), and there was virtually no change in transaminase activity (0·208 and 0·200) in her two biopsies.

Only 2 non-diabetic patients were investigated—1 with exfoliative dermatitis and a large liver (histologically normal and showing normal liver tests) and 1 with progressive muscular atrophy. In both the level of transaminase (0·146 and 0·170) was well below the mean initial level in the diabetic subjects, suggesting that there is increased activity in untreated diabetes.

Summary

Liver glutamic-aspartic transaminase activity was investigated in 19 diabetic patients before and after treatment of the diabetic state.

In 15 patients who were passing no sugar in the urine at the time of the second biopsy the mean level of transaminase activity was $0{\cdot}146 \pm 0{\cdot}013$ units, whereas before treatment the activity had been $0{\cdot}213 \pm 0{\cdot}011$ units. This difference is highly significant statistically.

There was no apparent relation between the initial level of transaminase activity or the change in activity and the type or duration of the diabetes or of the treatment given.

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References at foot of next column

POTASSIUM-SECRETING TUMOURS OF THE LARGE INTESTINE

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THE association of hypopotassæmia with villous tumours of the large intestine was not recorded until 1956, when a case was reported by Starr et al. Since then only four further cases have been recorded (Cooling and Marrack 1957, Goldgraber and Kirsner 1958, Jordan et al. 1958). It seems interesting, therefore, that two similar cases should come within the knowledge and care of us within eighteen months.

Case-records

Case 1.—A 70-year-old man was admitted to the Radcliffe Infirmary, Oxford, on May 4, 1956, gravely ill with severe diarrhœa. He gave a history of having passed about five stools daily for the past ten years—always loose, sometimes watery, frequently containing mucus, but never bloodstained. In the ten days before admission he had been passing copious watery mucus-containing stools at something like two-hourly intervals and had also had central colicky abdominal pain and had vomited.

On admission he was obviously dangerously ill; he was collapsed, severely dehydrated, and showed herpes labialis. The abdomen was soft and the rectum ballooned and empty.

Investigations.—Hb 82%, white blood-cells 14,000 per c.mm. Blood-urea 152 mg. per 100 ml. Serum chloride 70 mEq., sodium 115 mEq., potassium 3·2 mEq. per litre. Electrocardiography showed the typical depressed RST segment of hypokalæmia. The stools contained no pus cells or red blood-cells, nor could any pathogenic organisms be cultured.

Analysis of the rectal fluid showed an extremely high potassium content: chloride 112 mEq., sodium 122 mEq., and potassium 28 mEq. per litre.

Treatment.—Intravenous therapy was initiated with glucose, saline, and potassium chloride; and electrolytic stability was achieved after ten days. Sigmoidoscopy was then carried out, revealing a large polypoid mass at four inches. Several fragments were taken for histological examination and were reported as being derived from a rectal adenoma; the biopsy specimen being rather superficial, basal invasion could not be excluded.

On June 15, 1956, Mr. Elliot Smith removed an extensive papilliferous tumour of the rectum by a Hartmann's operation, leaving a terminal left-iliac-fossa colostomy; the patient made a rather slow, but eventually satisfactory, recovery. He remains (March, 1959) alive and well.

Pathology.—Examination of the specimen revealed a papillomatous growth, $4 \times 5 \times 10$ cm., with three small papillomas proximal to it. Sections of the main growth showed this to be a well-differentiated adenocarcinoma. The regional lymph-nodes were not involved.

Case 2.—A 56-year-old woman was admitted to the Western Infirmary, Glasgow, on June 30, 1958, in circulatory failure. She was confused and restless; her extremities were blue and cold and her eyes sunken. Her pulse was impalpable, and her blood-pressure could not be registered. From her relatives (later this was confirmed by the patient) was obtained a five-year history of " colitis ", which on questioning proved to be the passage of a clear watery rectal discharge several times a day. There was never any blood in the discharge, which had been slowly increasing in quantity. There had been no upset in her general health until six days before admission when she felt giddy and weak. She became progressively worse until, two days before admission, she was confused, weak, and unable to stand. The day before admission she vomited small quantities several times.

On admission rectal examination revealed the lower edge of a soft tumour encircling the lumen of the bowel. With the knowledge of case 1, villous papilloma of the rectum with excessive loss of water and potassium was diagnosed and an intravenous infusion of water, glucose, saline, and potassium chloride started. Serum levels twelve hours after admission were: sodium 128 mEq., potassium 3·4 mEq., and chloride 83 mEq. per litre; blood-urea 360 mg. per 100 ml.

Progress.—Rapid clinical improvement followed, and by the seventh day after admission serum levels were normal except for raised blood-urea (105 mg. per 100 ml.). The patient continued, however, to lose large quantities of fluid per rectum ($1^1/_2$–$2^1/_2$ litres daily) and she was unable to take adequate amounts of potassium chloride by mouth, with the result that the serum-potassium level fell again to 3·2 mEq. per litre, and was restored to normal only by an intragastric infusion of potassium chloride.

Further investigations.—Sigmoidoscopy showed a polypoidal tumour at five inches. Biopsy showed a well-differentiated papillary tumour which was regarded as premalignant. The rectal fluid was found to be a mixture of mucus and a watery solution. The mucus contained 1·8 mEq. per litre of potassium, while the solution contained sodium 122 mEq., potassium 17·6 mEq., chloride 141 mEq. per litre. A barium enema showed the upper limit of the tumour to be at the rectosigmoid junction and there was no evidence of obstruction.

Removal of tumour.—On July 29, 1958, the tumour was removed by an anterior resection. The patient recovered well from her operation and remains in good health (March, 1959).

Pathology.—The excised specimen consisted of a 10·0 cm. length of rectum. At each end there was a narrow cuff of normal mucosa, but the remainder of the mucosal surface showed a coarse irregular rugosity and was entirely covered by a low papilliferous growth. In addition there were three frondose polypi, each about 1·5 cm. in diameter, attached by narrow pedicles to the mid-portion of the specimen (fig. 1). Microscopic examination showed the lesion to be a well-differentiated papillary tumour of the rectal mucosa with much mucin-secreting activity (fig. 2). Although the tumour cells exhibited nuclear hyperchromatism and moderately numerous mitoses, there was no evidence of invasive growth. The appearances were those of a diffuse villous papilloma of the rectum (Ewing 1940).

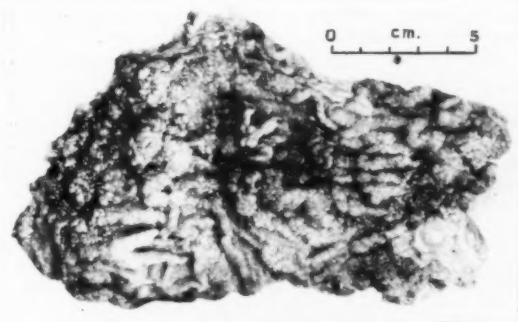

Fig. 1—Case 2: excised specimen of rectum, showing papilliferous growth and polypi.

DR. PATRICK, DR. TULLOCH : REFERENCES

Beaton, G. H., Curry, D. M. (1956) *Endocrinology*, **58**, 797.
Borel, C., Ryser, H., Frei, J. (1957) *Helv. physiol. pharm. Acta*, **15**, C12.
Bornstein, J. (1957) *Nature, Lond.* **179**, 534.
— Lawrence, R. D. (1951) *Brit. med. J.* i, 732.
Brin, M., McKee, R. W. (1956) *Arch. biochem. biophys.* **61**, 384.
Copenhaver, J. H., Shipley, E. G., Meyer, R. K. (1951) *ibid.* **34**, 360.
Donato, R. A. (1957) *Amer. J. clin. Path.* **28**, 377.
Gavosto, F., Pileri, A., Brusca, A. (1957) *Biochim. biophys. Acta*, **24**, 250.
Hugh-Jones, P. (1955) *Lancet*, ii, 891.
Karmen, A. (1955) *J. clin. Invest.* **34**, 131.
Patrick S. J. (1958) unpublished.
— Tulloch, J. A. (1957) *Lancet*, i, 811.
Rosen, F., Roberts, N. R., Budnick, L. E., Nichol, C. A. (1958) *Science*, **127**, 287.
Rossi, F., Tomatis, G. (1957) *Sperimentale*, **107**, 86.

Fig. 2—Case 2: microscopic appearance of rectal neoplasm (×75).

Discussion

This syndrome may be not so much rare as overlooked. These two cases and the five previously recorded resemble each other very closely. Villous tumours of the colon and rectum are not so very rare. In most cases the copious watery rectal discharge is the presenting and only symptom; and it is surprising that this syndrome has not been noticed more often.

Each case has presented as an emergency or has culminated in an emergency. Case 1 was admitted to medical wards, and there was some delay in deciding the cause of the patient's collapse. We should like to add villous tumours of the colon and rectum to the list of unusual causes of circulatory collapse.

It cannot be doubted that the fluid and electrolyte loss causes the collapse. The volume of fluid is presumably directly related to the surface area and size of the tumour. In neither case did we collect the secretion from the surface of the tumour, and so we can only speculate on the mechanism of the electrolyte loss. The potassium concentration in the rectal fluid ranged from 17·6 mEq. per litre in case 2 to 80 mEq. per litre in the case reported by Starr—i.e., from $3^1/_2$ to 16 times the concentration in plasma—whereas there is not the same deviation from normal in the values for sodium and chloride. This suggests an active secretion of potassium by the cells of the tumour. On the other hand, it is conceivable that the fluid secreted by the tumour is isotonic with plasma and the altered values are due to selective reabsorption by the colonic epithelium. Further study of these tumours may throw some light on the physiology of the colonic epithelium.

Summary

Two cases of circulatory collapse due to dehydration and hypopotassæmia caused by villous tumours of the colon are described.

Further study of these tumours may throw light on colonic epithelial function.

Our thanks are due to Mr. A. Elliot-Smith and Mr. A. B. Kerr for permission to publish; to Dr. A. H. T. Robb-Smith and Dr. A. J. Watson for preparation of the pathological specimens; and to Dr. W. H. Taylor and Mrs. R. I. Douglas for the biochemical estimations.

REFERENCES

Cooling, C., Marrack, D. (1957) *Proc. R. Soc. Med.* **50**, 272.
Ewing, J. (1940) Neoplastic Diseases; p. 732. London.
Goldgraber, M. B., Kirsner, J. B. (1958) *Gastroenterology*, **35**, 36.
Jordan, G. L., Erickson, E. (1958) *Arch. Surg., Chicago*, **77**, 248.
Starr, A., Mueller, S., McKittrick, J. R. (1956) *ibid.* **73**, 995.

Addendum

Since this paper was written we have studied two further villous tumours of the large intestine. In neither case was there any disturbance of the serum-electrolytes. In both cases fluid was obtained from the surface of the tumour. In the first case the fluid contained 96 mEq. sodium per litre, 54 mEq. potassium per litre, and 114 mEq. chloride per litre. In the second case the fluid contained 282 mEq. sodium per litre, 98 mEq. potassium per litre, and 538 mEq. chloride per litre.

TRAUMA AND SQUAMOUS SKIN CANCER

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THREE cases are here described in which a squamous epithelioma, proved histologically, developed within eight weeks of a traumatic incident.

If trauma is presumed to be a causal factor in the production of cancer, the following criteria, which were first stated by Ewing (1945), must be demonstrated:—

(1) The authenticity and the adequacy of the trauma.

(2) The previous integrity of the injured part.

(3) The tumour arises at the point of injury.

(4) A reasonable time-limit must be observed between the injury and the appearance of the tumour.

(5) The positive diagnosis of the presence and nature of the tumour.

These criteria apply to all cases of supposed traumatic cancer and not solely to skin cases.

The following three cases appear to satisfy Ewing's criteria.

Case-records

Case 1.—A man of 64 was, for most of his working life, outdoors, in the Navy and in H.M. Customs Waterguard. There was no family history of skin disease or cancer. His cancer developed on the face, six weeks after receiving an injury while picking cobnuts. The cancer developed at the exact spot at which the prick occurred—and the patient could not be shaken in this story. He was quite sure of the connection between the prick and the subsequent swelling.

The patient's skin was normal on unexposed areas, but rather dry and inelastic. On the exposed areas, his skin was thin, shiny, and inelastic, and on the face, smooth and relatively hairless.

Case 2.—In a man of 41 a cancer developed four weeks after a prick on the nose by a needle while he was sewing asbestos. The patient was a tough ex-regular soldier, who came of a rather poor home and spent five years in India with the Army. His other occupations were gardener, lagger, and electrician's mate on ships. There was no family history of cancer or skin disease.

The patient was quite certain of the connection between the prick on the nose and the subsequent warty growth which developed at the exact site of the prick four weeks later. Like case 1, the injury appeared to bear a definite relationship to the appearance of the cancer. Asbestos may have been implanted.

Case 3.—A woman of 63, while cleaning the chimney of her living-room fire, struck her right hand on a bracket at the back of the fire. Her hands at this time were contaminated by soot and soot got into the abrasion. She then washed her hands and continued at work without applying a dressing. A hard lump appeared in about three weeks, which grew rapidly until it was removed six weeks from the time of injury. This swelling was a grade-2 epithelioma showing well-marked infiltration of the deeper tissues. The rest of the skin of the patient's hands was within normal limits for her age.

The table shows the histories set out under five headings to correspond with Ewing's criteria.

TRAUMA AND SKIN CANCER

Case no.	Nature of trauma	Any previous lesion at site?	Did tumour arise at point of injury?	Time elapsing from trauma to histological diagnosis	Histological diagnosis	Comments
1	Prick on cheek while picking cobnuts	No	Yes	6 weeks	Squamous carcinoma	..
2	Prick by a needle while sewing asbestos cloth	No	Yes	8 weeks	Squamous carcinoma	Warty growth 4 weeks after injury
3	Struck back of hand on chimney projection, sustaining a soot-contaminated wound	No	Yes	6 weeks	Epithelioma grade 2	History of swelling 3 weeks after injury

Comment

It is necessary to accept the patient's statements for the first four of the five criteria, but as far as possible these statements have been crosschecked for time and other details. An attempt was also made to shake the patients in their stories, bearing in mind traumatic determinism—that is, that after the lesion appeared, the patient will come up with a story of injury. In each of these cases, the patient was quite sure that the injury was causally connected with the lesion.

In cases 1 and 2, the injury was a prick, and in case 2 asbestos implantation may have occurred. There is only one known case of skin cancer arising out of an asbestos corn (Wyers 1956). It is considered unlikely that case 2 involved an asbestos corn.

The time interval until histological diagnosis is of interest—six weeks in two and eight weeks in one. The lesion was noted in three weeks in one case and had been present in each of the other cases for about two weeks before removal and section. The close correlation of the three times and the short time interval from trauma to cancer seems to be of importance. The time interval from the injury to the appearance of a squamous cancer in the case of a petroleum worker who cut the dorsum of his hand and sustained a severe blow on the slowly healing wound described by Kotin and Kohler (1953) was one month and this correlates well with the above cases. In animals which had been painted with a very strong carcinogen, Pullinger (1945) was able to localise tumours by wounding. The observed connection between burns, scars, and skin cancers is well known.

The role of trauma in the production of squamous skin cancer is probably that of a cocarcinogenic stimulus—that is, a stimulus which of itself cannot produce a cancer but which will accelerate, promote, or bring to fruition the appearance of a cancer in a cell in which the initiation of a cancer had been produced by a carcinogen (or initiator).

Henry (1950) and Mackee and Cipollaro (1937) call attention to the frequency with which burn scars are followed by skin cancer and quote the 2000 cases reported by Neve (1923) of cancer due to the carrying of portable fire baskets in Kashmir. Schreck (1941) in a review of cutaneous cancer showed that 18% of tumours of the scalp, trunk, legs, and arms developed in scars resulting from injury, burns, lacerations, operations, and ulceration, and that 2·8% of all the tumours arose in scars. In contrast 0·7% (3 cases) of 443 tumours of other sites occurred in scars. In Broders (1921) series of epitheliomas, there was a history of burning in 24%.

Summary

In three cases of histologically proved squamous skin cancer recent trauma—within two months—was believed to be of importance in the ætiology. Trauma probably acts as a cocarcinogenic stimulus.

I wish to thank Dr. A. G. C. Taylor and Dr. T. K. Morgan, of the radiotherapy department of the Royal South Hants Hospital, for allowing me to see their cases.

REFERENCES

Broders, A. C. (1921) *Amer. Surg.* **2**, 141.
Ewing, J. (1935) *Arch. Path.* **19**, 690; *Bull. N.Y. Acad. Med.* **11**, 281.
Henry, S. A. (1950) *Ann. R. Coll. Surg. Engl.* **7**, 425.
Kotin, P., Kohler, J. E. (1953) *Cancer, N.Y.* **6**, 266.
Mackee, G. M., Cipollaro, A. C. Cutaneous Cancer and Precancer. New York, 1937.
Neve, E. F. (1923) *Brit. med. J.* ii, 1255.
Pullinger, B. D. (1945) *J. Path. Bact.* **57**, 467.
Schreck, R. (1941) *Arch. Path.* **31**, 434.
Wyers, H. (1956) *Trans. Ass. industr. med. Offr.* **6**, 24.

UNEXPECTED HAZARD OF ANÆSTHESIA

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THE presence of foreign bodies in anæsthetic apparatus, causing obstruction to the airway, has been reported from time to time. The following case demonstrates that an artificial airway may be obstructed even after the most careful preoperative inspection of apparatus.

Case-report

A secundigravida was admitted to St. Mary's Hospital, Manchester, for elective cæsarean section on account of rhesus incompatibility. After premedication with atropine 0·6 mg. intramuscularly the patient was brought to theatre. The Boyle's anæsthetic machine was carefully inspected, gas cylinders were turned on, and corrugated delivery tubing and catheter mount were connected and tested—gas flowed freely at the distal end. A cuffed no. 8 Magill tube was selected from several similar tubes and the integrity of the cuff confirmed with a syringe. A brass stylet 4·5 mm. in diameter was passed through the tube via a Cobb's suction union to act as a stiffener. The slight resistance encountered to the passage of the stylet down the tube could easily be accounted for by the lack of lubricant and the difference in curvature of the stylet and tube.

The efficiency of the Mackintosh laryngoscope having been confirmed, anæsthesia was induced with 200 mg. of 5% thiopentone, this being followed as soon as the patient was unconscious by suxamethonium chloride 50 mg. The patient was ventilated with oxygen via a mask and then intubated with the aforementioned Magill tube.

On connecting the corrugated delivery tubing to the endotracheal catheter, it proved impossible to inflate the patient, who, however, remained satisfactorily pink throughout the manœuvre, owing to the previous inflation with oxygen. After one or two moderately forceful but ineffectual compressions of the reservoir bag, it was thought that the failure of the thorax to inflate might be due to extreme bronchospasm. Before acting on this assumption, and despite the satisfactory results of the preoperative inspection of apparatus, it was decided to change the endotracheal tube and Cobb's union. A fresh tube and union was quickly procured and the patient was reintubated.

Endotracheal tube containing cleaning-brush.

Inflation was then found to be normal. No further difficulty was experienced, and the operation was completed uneventfully.

The patient having been returned safely to the ward, the tube was slit up its length and, as the accompanying figure shows, it was found to contain half of a Magill-tube cleaning-brush, the wire of which had obviously broken during cleaning, unnoticed by the nurse or orderly concerned. The brass stylet could be passed apparently freely down the tube alongside the broken brush, which was itself stuck fairly firmly to the wall of the tube. The tube might have been cleaned by any one of several persons during the period of perhaps several weeks before the tube was used; and subsequent inquiries failed to disclose the person responsible.

Discussion

In recent years several similar mishaps have occurred, in each case the impossibility of inflation seeming almost inexplicable.

Rollason (1956) reported a case in which the T-junction of a Cobb's suction union was imperforate although the union freely admitted a stylet, and he knew of a second, exactly similar, case. Langton Hewer (1956) mentioned a case in which the plastic spigot from a rubber face-mask had found its way into a Cobb's union and caused a valvular obstruction, permitting expiration but not inspiration. Stoneham (1957) reports the accidental blocking of an oral airway with pledgets of cotton-wool which had mistakenly been used to clean it. Haselhuhn (1958) describes the occlusion of the lumen of an endotracheal tube by a foreign body, later found to be a rubber tip used over the adaptor of the Abbott ' Venopak '.

In two out of these four reports, the difficulty of inflation was ascribed in the first instance to intense bronchospasm. In Rollason's case, where the patient had very severe emphysema and chronic bronchitis, gallamine was given in a dose of 80 mg. in the hope of alleviating the supposed spasm. In the present case also, the possibility of intense bronchospasm was momentarily considered. Inquiries among anæsthetist colleagues, however, indicate that bronchospasm of such acute onset and of such severity must be very rare indeed. It would seem therefore wiser in the event of a complete or almost complete obstruction of this nature to assume in the first instance that it is due to some defect in the apparatus and quickly to change any airways or tubes, even if these have been tested and thought to be satisfactory immediately before the operation.

In the present case the fact that the patient's condition caused no real anxiety must be ascribed to the thorough ventilation with oxygen before the attempted intubation; and the case emphasises the great value of this procedure as a routine of induction of anæsthesia.

At St. Mary's Hospital, all endotracheal tubes after being cleaned with the Magill brush are now, as a precaution, threaded with a piece of tape which is then knotted, to show the patency of the tube.

My thanks are due to the department of medical illustration, Manchester Royal Infirmary, for the photograph, and to Dr. H. J. Brennan for helpful criticism.

REFERENCES

Haselhuhn, D. H. (1958) *Anesthesiology*, **19**, 561.
Hewer, C. L. (1956) *Brit. med. J.* ii, 766.
Rollason, W. N. (1956) *ibid.* p. 658.
Stoneham, F. J. R. (1957) *ibid.* i, 400.

CYSTIC DEGENERATION IN A DISCOID MEDIAL CARTILAGE

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A DISCOID internal meniscus is found normally in the lizard and chimpanzee, but in man this condition is rare. Apparently only one case of cystic degeneration in a discoid internal meniscus has been reported (Smillie 1948). I describe here a further case.

In 1930 Watson-Jones reported a possible case of discoid medial meniscus; but the first undoubted case was described by Cave and Staples in 1941. In 1945 Dwyer and Taylor described a case, and Jeannopoulos (1950) reported a case of discoid medial and lateral menisci in the same knee. Smillie (1948), Richmond (1958), and Ross et al. (1958) added further cases; in one of Smillie's cases cystic degeneration was present.

Case-report

A man, aged 26, had a swelling on the medial aspect of the right knee, which had very slowly become larger since he had first noticed it three years previously. There were no other symptoms referable to the knee.

On examination the swelling, which was just below the joint and anterior to the medial ligament, was about the size of a walnut and firm, and appeared to be less tense with the knee flexed than extended.

At operation (Mr. A. G. O'Malley) on Feb. 6, 1957, a discoid medial meniscus with widespread cystic change was found. The meniscus was removed, but unfortunately, owing to operative difficulties, the specimen was damaged, and it had to be stitched before being mounted (fig. 1). The postoperative

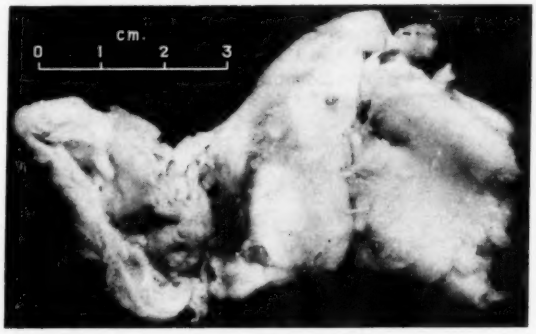

Fig. 1—The excised specimen.

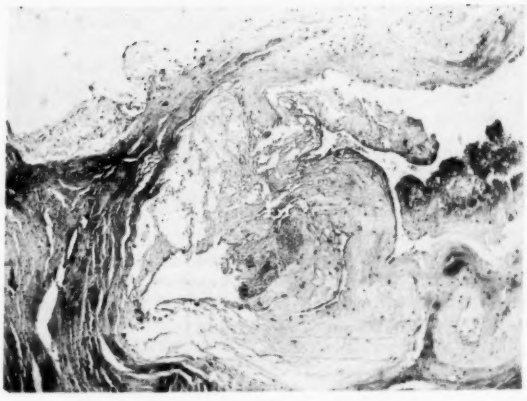

Fig. 2—Photomicrograph of specimen (x 460).

course was uneventful, and the patient is now symptom-free and at work.

Pathological Examination

The excised tissue showed a discoid meniscus with pronounced cystic degeneration arising from the periphery and most severe anteriorly. There was horizontal cleavage. The specimen appeared to be of the type described by Smillie (1948) as primitive, in which the cartilage is a complete plate with a thick free margin which may be convex.

Microscopic examination showed fibrous tissue undergoing degeneration with areas of amorphous necrotic acellular tissue without inflammatory reaction. In other areas fibrous tissue had broken down and formed a loose network. The cystic areas were lined by fibrous tissue. Degenerative cartilage cells merged imperceptibly into dense fibrous tissue (fig. 2).

I wish to thank Prof. Bryan McFarland for his guidance and advice, Mr. A. G. O'Malley for permission to describe this case, and Dr. C. A. St. Hill for a histological report on the section.

REFERENCES

Cave, E. F., Staples, O. S. (1941) *Amer. J. Surg.* **54,** 371.
Dwyer, F., Taylor, C. (1945) *Brit. med. J.* ii, 287.
Jeannopoulos, C. L. (1950) *J. Bone Jt Surg.* **32A,** 649.
Richmond, D. A. (1958) *ibid.* **40B,** 268.
Ross, J. A., Tough, I. C. K., English, T. A. (1958) *ibid.* p. 262.
Smillie, I. S. (1948) *ibid.* **30B,** 671.
Watson-Jones, R. (1930) *Proc. R. Soc. Med.* **23,** 1588.

DEMONSTRATION OF PLASMA FIBRINOGEN BY PAPER ELECTROPHORESIS

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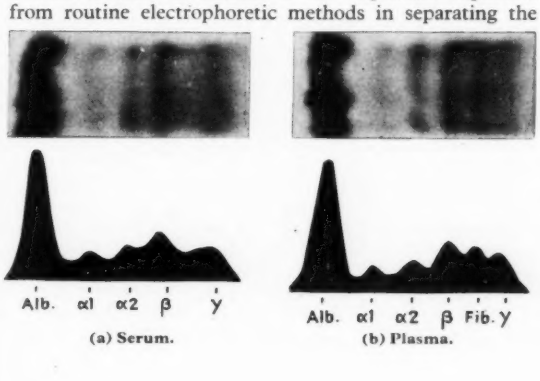
PLASMA is usually considered to be unsatisfactory for the analysis of blood proteins by paper electrophoresis because fibrinogen confuses the pattern in the gamma-globulin/beta-globulin region (Flynn and De Mayo 1951, Flynn 1954). No reliable method for the separation of these three fractions has been described. Hence serum is almost always used in routine laboratory practice, although plasma may be more readily available. Moreover, an indication of the fibrinogen content provides useful additional information.

The following method has been developed in this laboratory for use with an 'EEL' electrophoresis apparatus:

The buffer solution, pH 8·6, consists of sodium barbitone 30 g.; sodium acetate (hydrated) 19·5 g.; 0·1 *N* hydrochloric acid 205 ml.; made up to 3 litres with distilled water. The paper, Whatman no. 1, 5 × 40 cm., is soaked in the buffer solution. Heparinised plasma, which must be completely free of hæmoglobin, is applied along a 'Perspex' straight edge from a glass capillary tube. Electrophoresis proceeds for 24 hours at 8 mA and at the end of this time the polarity is reversed and the current increased to 12 mA for 1½ hours.

This reversal of current is the important departure from routine electrophoretic methods in separating the fibrinogen fraction. The times and amperages stated have given good results, but they are not critical, and will undoubtedly vary with different types of apparatus and solutions.



(a) Serum. (b) Plasma.

Papers are dried at 90°C. The stain is a matter of personal choice; that used here is bromphenol-blue, followed by a modification of the washing method of Jencks et al. (1955). This consists of three washes in 2% acetic acid, and finally a quick wash, till darkening occurs, in 0·2% sodium acetate in 1% acetic acid. The papers are then blotted, redried at 90°C, and given a final wash in a mixture of equal quantities of acetone and ether.

The separation of the fibrinogen band from the globulins can be seen in the figure.

REFERENCES

Flynn, F. V. (1954) *Proc. R. Soc. Med.* **47,** 827.
— De Mayo, P. (1951) *Lancet*, ii, 235.
Jencks, W. P., Jetton, M. R., Durrum, E. L. (1955) *Biochem. J.* **60,** 205.

ECZEMA HERPETICUM (KAPOSI'S VARICELLIFORM ERUPTION) IN AN ADULT

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ECZEMA herpeticum is uncommon in adults, and the recorded cases almost always have a history of Besnier's prurigo in childhood, or some form of eczematous lesion later in life. Brain (1956), reviewing the manifestations of herpes-simplex infection, recorded only 1 example of eczema herpeticum in an adult in his series of 37 cases. Ruchman et al. (1947) found 96 cases in the literature, of which only 21 were adults, and these adult cases had a mortality of 9%.

Case-report

A German student of 18, on holiday in England, was admitted to hospital on Aug. 1, 1958. He had a history of Besnier's prurigo since the age of 3 months, with recurrent attacks of eczema affecting particularly his face and neck. Certain foods such as coffee, eggs, and spices precipitated an attack. He had been subject also to attacks of asthma since early childhood. There was no history of previous herpes-simplex infection, and he had not been treated recently with corticosteroids.

Two days before he had noticed a red irritating non-vesicular rash of his upper lip, associated with slight swelling. Although previously eczema of his face had been made worse by exposure to bright sunshine, he continued his holiday activities, including swimming and sunbathing. During the next two days he felt burning and itching of his face and chin, and a severe weeping eruption broke out over the whole head and neck. This was worse over the face and front of his neck. There was so much œdema that he could see only with difficulty between his eyelids.

Examination

He was a well-built fair-haired man, who looked ill and had a fever of 102·5 F. His œdematous face and neck were covered with a confluent weeping eruption of such severity that a sero-purulent exudate ran down his neck, and his hair was matted with dried exudate. The rest of his skin was slightly scaly and lichenified, especially in the flexures. There was a moderate submandibular and cervical lymphadenitis, the glands being tender. He had a purulent conjunctivitis.

At this stage he presented the picture of severe acute infective dermatitis.

Progress and Treatment

He was given tetracycline 250 mg. 4-hourly. Normal-saline compresses were applied to the face and neck before neomycin and hydrocortisone lotion (1%) were used locally.

The day after admission to hospital there appeared on his nose, and in a band about 10 cm. wide round the base of his neck and upper chest, multiple (almost confluent) lesions about 3 mm. in diameter. These were either umbilicated varioliform pustules, or tiny red shallow punched-out pits exuding serum. These more characteristic lesions enabled the diagnosis of eczema herpeticum to be made. Gamma-globulin 1·5 g. was given intramuscularly.

2 days later most of the lesions had dried, and the seropurulent crusts readily dropped off his face and neck. The facial œdema and general toxicity were diminished, though his evening temperature was 101°F, and he was still very ill.

He was anxious to return with his holiday group to Germany, and next day we reluctantly allowed him to leave hospital and to travel. By then he was apyrexial, and his skin condition was improving rapidly. After discharge he made an uninterrupted recovery, and he was able to resume his studies two weeks later.

Investigations

Swabs from the lesions grew coagulase-positive *Staphylococcus aureus*, and Lancefield group-A hæmolytic streptococci; virus culture on chick embryo grew the herpes-simplex virus. The white-cell count was 9700 per c.mm. (73% polymorphs, 21% lymphocytes, 3% monocytes, 1% eosinophils, and 2% Türk cells). His chest radiograph was normal.

Conclusions

The outstanding features of this case were the rapid onset and severe general toxicity which accompanied the eruption. The diagnosis was obscure at first because of the confluent exudative lesions and the infection. But next day the characteristic weeping varioliform lesions, associated with œdema and secondary pyogenic infection, and with regional adenitis, was in keeping with Kaposi's (1887) classical description. Isolation of the herpes-simplex virus by culture confirmed the diagnosis.

It is of interest that there were no untoward effects of his premature discharge from hospital only four days later.

I should like to thank Dr. R. T. Brain, under whose care the patient was admitted, for his advice and help in preparing this paper.

REFERENCES

Brain, R. T. (1956) *Brit. med. J.* i, 1061.
Kaposi, M. (1887) *Vjschr. Derm. Syph., Wien*, **14**, 273.
Ruchman, I., Welsh, A. L., Dodd, K. (1947) *Arch. Derm. Syph., Chicago*, **56**, 846.

Preliminary Communication

URINARY ACIDIFICATION DEFECT IN CHRONIC INFANTILE MALNUTRITION

THE ability of the kidney to lower the urinary pH after an acidifying stimulus depends on the maintenance of a hydrogen-ion (H^+) gradient across the renal tubular cell, and requires intact cellular mechanisms. It is characteristic of potassium deficiency that this gradient cannot be maintained.[1]

In view of the known intracellular disturbances in severe chronic malnutrition in infants,[2] it was thought likely that some acidification defect might be demonstrable.

In 7 malnourished children, ammonium chloride was given orally (in a dose of 0·1 g. per kg. body-weight)[3] immediately on admission and again after recovery. The accompanying table shows that on admission this dose did not make the urine as acid as it did later.

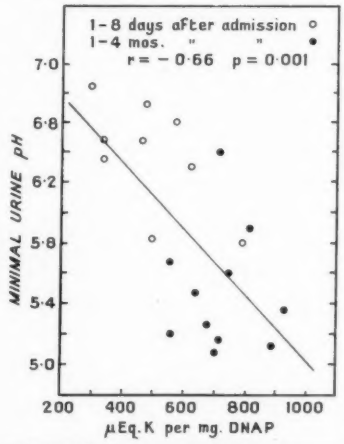
MINIMAL URINARY pH AFTER AMMONIUM CHLORIDE (0·1 G. KG. BODY-WEIGHT) IN SEVEN MALNOURISHED CHILDREN

Patient	Age in months (on admission)	pH		Time between observations (days)
		On admission	During recovery	
M. Ck.	10	6·06	5·50	52
J. W.	12	6·71	5·35	67
M. Ce.	13	5·80	5·11	41
E. G.	13	5·83	5·08	62
R. G.	11	6·49	5·60	45
B. S.	18	6·48	5·46	89
L. McB.	12	6·60	5·55	78

In other malnourished children, ammonium chloride was given at various stages during recovery, and its administration was preceded by a muscle biopsy. The relation between the muscle-potassium content, expressed as μEq. K per mg. deoxynucleic acid phosphate (D.N.A.P), and the lowest urinary pH is shown graphically in 20 observations. D.N.A.P. is used as the most reliable standard of reference.[4] The correlation is highly significant ($P = 0·001$).

DISCUSSION

The ability to concentrate H^+ ion is a tubular function which is probably as well developed in infants as in adults.[5] When a standard acid load is given, the lowest pH reached by the urine is a measure of the efficiency of this function, and is largely independent of factors such as glomerular filtration-rate and renal plasma-flow which are said to be altered in chronic infantile malnutrition.[6] The supply of H^+ appears to depend on the availability of CO_2 produced by the kidney[7]: theoretically it could be limited either by a reduction in substrate, CO_2, or by a depression of intracellular carbonic anhydrase.



Relationship between potassium content of muscle, expressed as μEq. K/mg. D.N.A.P., and minimal urinary pH after administration of ammonium chloride.

Assuming that the *production* of H^+ is not the limiting factor, it seems probable that the failure to *concentrate* available H^+ was due to potassium deficiency (see figure).

It is not clear whether this renal functional disturbance plays any part in the acid-base balance in these children. In the absence of severe diarrhœa, systemic acidosis does not occur; nor would it be expected as a consequence of inability to excrete a urine of low pH, unless ammonium excretion was also impaired.

I am indebted to Dr. Oliver Wrong, who suggested this investigation when he visited the West Indies with the support of the Colonial Medical Research Committee, and to Dr. John Waterlow for his advice and encouragement.

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B.A., M.B. Cantab.

1. Clarke, E., Evans, B. M., MacIntyre, I., Milne, M. D. *Clin. Sci.* 1955, **14**, 421.
2. Frenk, S., Metcoff, J., Gomez, F., Ramos-Galvan, R., Cravioto, J., Antonowicz, I. *Pediatrics, Springfield*, 1957, **20**, 101.
3. Davies, H. E. F., Wrong, O. *Lancet*, 1957, ii, 625.
4. Waterlow, J. C., Mendes, C. B. *Nature, Lond.* 1957, **180**, 1361.
5. McCance, R. A., von Finck, M. A. *Arch. Dis. Childh.* 1947, **22**, 200.
6. Gordillo, G., Soto, R. A., Metcoff, J., Lopez, E., Antillon, L. G. *Pediatrics, Springfield*, 1957, **20**, 303.
7. Roberts, K. E., Poppell, J. W., Randall, H. T. *Fed. Proc.* 1956, **15**, 153.

Reviews of Books

Chemical Prevention of Cardiac Necroses

HANS SELYE, M.D., PH.D., D.SC., professor and director of the Institute of Experimental Medicine and Surgery, University of Montreal. New York: Ronald Press. 1958. Pp. 235. $7·50.

THE chemical prevention of cardiac necroses is the latest development of Selye's hypothesis of the " diseases of adaptation ". It is perhaps the most exciting and certainly the best supported of the many outgrowths of this fertile concept. The dominant theme of this book is that " electrolytes, steroids and stress all play important conditioning roles in the development of cardiopathies elicited by the most diverse agents ". The diversity of these agents is reflected in the list of headings under which they are considered—namely, electrolytes, hormones, vitamins, cardiac glycosides, chemical compounds and food constituents, physical agents, psychic and nervous stimuli, microbes and their toxins, hypersensitivity, spontaneous diseases, and " various and other factors ".

Since the views advanced embrace the most important part of cardiac pathology it is reassuring to find that they are based on sound animal experimentation, as well as a phenomenal acquaintance with world literature. Despite the overwhelming mass of facts derived from these two sources, the book is easy to read, and its implications both fascinating and stimulating. It should be read by every practising cardiologist, and since cardiac necrosis is probably the commonest cause of death in man we hope that many others will read it too.

Family Influences and Psychosomatic Illness

E. M. GOLDBERG, of the social medicine research unit of the Medical Research Council. London: Tavistock Publications. 1958. Pp. 308. 38*s*.

THIS investigation of the family background of 32 young men with duodenal ulcer is based on the hypothesis that psychological and social factors may have contributed to the increased incidence of duodenal ulcer, and that these factors are associated with changes in the composition of the family, in relationships within the family, and in the methods of bringing up children.

The material for the study consisted of 32 men with duodenal ulcer, aged 16–25, attending two East London hospitals who were matched for age with a control series of 32 men from the register of a general practitioner. A psychiatrist, a psychologist, and Miss Goldberg, a psychiatric social worker, investigated the subjects and their families. The most important findings concerned the roles of the parents of the patients with duodenal ulcer, especially the mothers, who were characteristically obsessional and striving, themselves prone to psychosomatic illnesses, and with tendencies to overprotect, to restrict, and to overindulge their children. Typically, the fathers were quiet and mild, more attentive to their sons when young but as the sons grew up figuring less as models than as " pals ". The fathers often had themselves suffered from dyspepsia or ulcers. The patients had been gentle and unaggressive boys with especially close ties to their mothers. The parental homes had been stable and the family bonds close, the mother playing a dominant role as organiser and authority figure.

Most striking, perhaps, were the similarities between the family background of the ulcer group and the controls, which suggest that the changing roles of men and women in the modern urban family may be universal and only intensified in those families that breed sons with duodenal ulcers. As Miss Goldberg remarks, the increasing authority of the mother may lead to considerable problems of identification in the growing son, and the incompatibility of his strong tie to his mother with the demands that the outside world makes upon him may cause severe conflict in the young man. The research was undertaken by the social medicine research unit of the Medical Research Council, and in a later volume it is hoped to relate these familial and childhood factors to the emergence and functioning of the adult personality.

Staphylococcal Infections

IAN MACLEAN SMITH, M.D., F.R.F.P.S., assistant professor of medicine, State University of Iowa. Chicago: Year Book Publishers. London: Interscience Publishers. 1958. Pp. 180. 32*s*.

MANY papers, conference reports, leaders, and annotations scattered throughout the medical journals discuss the epidemiology, prophylaxis, diagnosis, and treatment of staphylococcal infection as it occurs today. This short textbook is an attempt to give the gist of this information in an easily accessible form. It is thoroughly up to date (the useful section on antibiotics includes even ristocetin and kanamycin) and although a small book of this kind cannot probe very deeply, selected British and American references with each chapter should help the reader to fill in detail.

Calcium Requirement and Adaptation in Adult Men

OLE J. MALM, Johan Throne Holst Institute for Nutritional Research. Oslo: Oslo University Press. 1958. Pp. 290.

FOR many years Professor Nicolaysen and his associates in Oslo have been pioneers in the study of calcium metabolism; one of their major contributions has been the new concept that people can adapt to a low intake of calcium by an increase in their ability to absorb calcium from the gut. In this volume (published also as a supplement to the *Scandinavian Journal of Clinical and Laboratory Investigation*) Dr. Malm has brought together much of the work on which this theory is based. The balance studies which were made on volunteers from the State prison are exceptionally valuable because they extended over many months; and they may provide a new basis for estimating the calcium requirements of normal adult males.

An aspect of the work of special interest to the clinician concerns the relation of the intake of calcium to the production of senile osteoporosis. This condition is usually thought to be the result of diminished osteoblastic activity, but it seems that a simple lack of calcium without deficiency of vitamin D can account for some instances of senile osteoporosis, presumably in people who have lost their ability to adapt to low intakes. The book contains an extensive bibliography complete with the titles of papers.

Reversicon: A Medical Word Finder

J. E. SCHMIDT, PH.B.S., M.D., LITT.D., president, The American Society of Grammatolators; chairman, National Association on Standard Medical Vocabulary. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958. Pp. 440. 57*s*. 6*d*.

Humpty Dumpty and the Red Queen must have thought up between them this looking-glass dictionary, in which one searches for unknown words, each *vox* supplying the reciprocal of a definition—just the thing for a writer at loss for a word. The non-technical writer could, of course, turn to Roget's *Thesaurus*, and even then he would not be sure of finding exactly the right word. This work is not confined to medicine but embraces, among other things, nursing, pharmacy and pharmacology, chemistry, botany, and zoology. American usage is followed, which means not only that some things are called by different names and some spelt differently from English but also that many of the listed words do not exist in this country.

It's Healthy to be Human (London: British Medical Association. 1958. Pp. 160. 10*s*. 6*d*.).—The slightly ambiguous title of this *Family Doctor* book does not mean that *homo sapiens* has a special endowment of health but that it makes for health to recognise and be kind to our instincts. This thesis Dr. F. R. C. Casson expounds persuasively, with knowledge, tolerance, insight, and humour, supporting and illustrating it with well-chosen examples. Normal psychological development is sketched from babyhood to age, and the nature, power, manifestations, and modifications of the sexual and the self-assertive instincts are the book's main theme. That man cannot live by bread alone is implicit throughout the book; whether he can live a life worth living without a

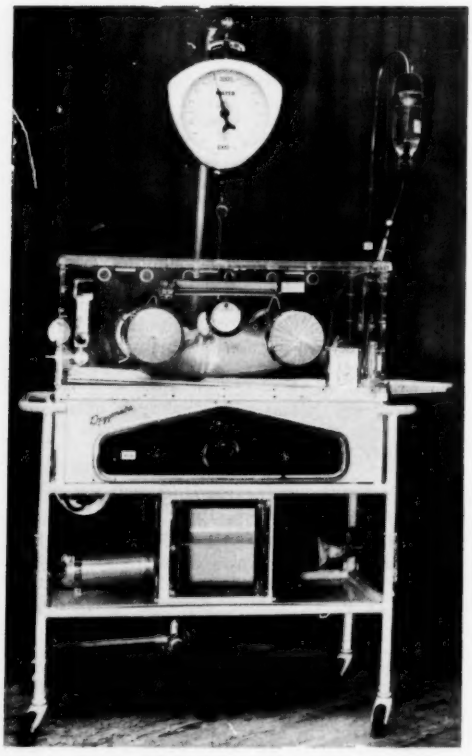
Credo or scheme of values is not considered, and mention or recognition of the " herd instinct ", as expounded by Wilfred Trotter, is so conspicuously absent that the hunting in packs of dogs " in the wild state " is ascribed to intelligence subduing instinct. A chapter on Are Doctors Human ? is disappointing, at least to a doctor; but the book can be warmly recommended as a provoker of thought and fund of good advice to the " ordinary reader ", for whom it is intended, especially if he is young and a parent.

Modern Treatment Year Book 1959 (25th ed. London: Baillière, Tindall, & Cox, for *The Medical Press*. 1958. Pp. 312. 30*s*.).—Twenty-five editions and acclamation from all over the world seem adequate comment on this book, edited by Sir Cecil Wakeley. Yet the preface says that it is intended to help the general practitioner, and readers of the 1959 volume may wonder whether some articles will do that. There are excellent articles—the one on carcinoma of the rectum and colon is outstanding—and there are topics very relevant to a general practitioner's work (chronic bronchitis and painful feet, for example). But there is much that is beyond a family doctor's (and many specialists') scope. Is the management of spina bifida cystica and hydrocephalus or technical details of the treatment of endocrine crises a necessary part of a general practitioner's knowledge ?

New Inventions

AN INCUBATOR BALANCE

THE spring balance shown in the accompanying figure is designed to weigh an infant up to 6000 g. with an accuracy of ±2·5 g. while it is being nursed in an incubator. Rapid and frequent weighings are possible.



POSTOPERATIVE WEIGHT AND FLUID RECORD: HUMIDITY 98% (RECORDED ON INSTRUMENT IN INCUBATOR); TEMP. 80°F IN INCUBATOR 'ALEVAIR' MIST; NO FLUIDS BY MOUTH

Hr. after operation	Pleural drainage (ml.)	Intravenous fluids (ml.)	Urine	Stools	Fluid balance (ml.)	Weight (g.)
1	..	..	..	..	..	3665
4½	5	Blood 80; 5% dextrose 25	..	..	+100	3665
9½	15	5% dextrose 120	..	..	+105	3760
57	..	½ strength plasma in 2·5% dextrose from 10th to 34th hr., 237	Passed 2-hrly	10	..	3625

A spring balance has been chosen because it is simple to read, is accurate, and has a very stable zero in conditions of rough treatment, heat, and moisture. It is not expensive.

The makers have adapted a standard model [1] so that each revolution of the pointer records 2000 g. in 5 g. divisions to a maximum of three revolutions. The second and third revolutions are shown on the bottom slide. A long hook connects the balance with the infant's sling through a 1 in. hole in the 'Perspex' top of the incubator. The balance is adjusted by the manufacturer to read zero with the hook and sling attached. The incubator we use [2] has an infant-weighing sling provided (this is easily sterilised). The perspex ice box is omitted. The hospital engineers made the stand. This has three legs of ample length for stability. The 6-foot tubular upright is adjustable for height and carries a horizontal arm supporting the balance above the incubator.

Tubing for transfusion, drainage, and feeding extends from the baby through holes in the incubator walls. This tubing does not affect serial weighings if the loops of tubing are not altered greatly in length. The same splint is used all the time for the limb into which a transfusion is being given.

The movements of infants cause far less oscillation of the pointer than was expected. Gently swinging the infant in its sling often puts it to sleep. If movements are excessive, there is always a period when the infant is still; and, as the needle steadies immediately, a reading can be taken. For serial weighings at short intervals, the infant is left lying on the sling (which is merely a sheet of plastic).

To weigh an infant, the balance is lowered so that the hook extends through the lid of the incubator far enough for the rings on the sling to be attached. The balance is raised till the infant is suspended freely. Readings can be made with the minimum of disturbance to the infant and may be started immediately after an operation is completed. Two-hourly weighings of an infant in the incubator at 81°F and 98% humidity (recorded by the instrument in the incubator), receiving nothing by mouth, were 3345, 3330, 3305, and 3295 g. No urine or stools were passed during this time. The weights show the water-loss clearly over six hours. The accompanying table shows part of a postoperative record of weighings. Weight stayed constant while operative losses were restored; then intravenous fluids exceeded requirements for a few hours; and this was followed by satisfactory balance as the excess fluid was lost.

With this balance the weight changes of infants can be followed accurately under practically any conditions. The method should prove useful in the management of fluid therapy.

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A Time Abroad

MOST people are now well aware that a period of medical work in Africa, or the West Indies, or Hong Kong can be a satisfying and enlightening experience, as well as an exciting one. But, thinking perhaps of small overcrowded hospitals and crowds of "primitive" patients, they underestimate the new opportunities for practising medicine and surgery at a high level, and especially for investigation. They do not know that the wonderful 500-bed Nigerian hospital at Ibadan, with over 60 registrars and house-officers, is becoming an important medical centre; or they fear that, if they go there for two or three years, their seniors, who make the consultant appointments, will still be thinking in terms of the past. At last, however, the idea that work abroad is in some way less creditable than work at home is on the way out; and already two members of the staff of the University College of the West Indies have been appointed to professorial chairs in London. The time must surely come when (in this matter at least) reason will triumph over prejudice, and posts will be given more readily to men who have been abroad than to those who have not.

The remarkable development of the university colleges of the Colonies owes much to their "special relationship" with the University of London: on the recommendation of the Asquith Commission in 1943, London University accepted, as an interim measure, an arrangement whereby its teaching standards would be maintained in the colleges, and London degrees would be awarded by special examinations. "A University College", said the commission, "must encourage the pursuit of a regular and liberal course of education, promote research and the advancement of science and learning . . ." and a great deal has been done to realise this ideal. In Jamaica the University College Hospital has been recognised by London University since 1952, and the number of students who have qualified as M.B. is approaching 100. Under present plans the college will attain independent university status in a few years, after which (like Hong Kong or Malaya) it will award its own degrees—in medicine as well as other faculties. During this preliminary period the college has, of course, owed much to physicians and surgeons who have gone out from this country, despite financial disadvantage, and have started the medical teaching, as well as much first-rate research.

In the newer medical school at Ibadan the clinical teaching has only recently been recognised for London degrees. In his account of the University College of Nigeria,[1] Dr. KENNETH MELLANBY, first principal of the college, describes the astonishing transition from the Government medical school at Yaba in Lagos to the great new hospital, whose flourishing medical school had an intake of 50 preclinical students last year. It is an indication of the progressive outlook of the people of Nigeria that their elected Federal Government has spent nearly £5 million on this project, and a measure of the importance they attach to medical education that so large a proportion of Nigeria's total revenue should be voted to this purpose. The fact that in a country with a population of 32,000,000 there is only one doctor for well over 50,000 people shows how much remains to be done in this direction. Meanwhile here, as in other overseas territories, the possibilities for original research, of many different kinds, are immense; and the new school and hospital at Ibadan now provide facilities of a high order, and space which would be envied by many investigators in this country. As regards clinical material, the main difficulty, as in other developing countries, is to limit numbers. For the registrar, a year or more of work in such surroundings provides fresh experience, a training in self-reliance, and an outlook on medicine which can hardly fail to be of help. In senior posts there is great need for consultants in special subjects—in particular dermatology, ophthalmology, psychiatry, and pædiatrics. For many years to come there cannot be enough trained Nigerian postgraduates to fill all the specialist appointments, and it is during these years that reinforcements from this country will be particularly valuable. Even thereafter, the closer the exchange between such hospitals as Ibadan and the teaching hospitals here, the more advantage may accrue to both, and the greater the contribution British medicine will make to the countries which need its help.

If there are young specialists who are needed abroad and would like to go, and would be better doctors or research-workers for going, must we indefinitely condone a system which makes it so difficult for them to leave this country? Must we accept the ironical conclusion of Apollodorus [2] that "so many groups of people would benefit from the plan that it is very unlikely to come about"? Several possible ways of removing the obstacles were discussed at a conference convened by the British Medical Association last November [3]—notably (1) secondment from the National Health Service, (2) supernumerary posts, and (3) the proleptic appointments so ably advocated by Prof. CHARLES WELLS.[4] All the arguments for and against each plan, were admirably stated, and the conclusion was plain—that they could all be useful in their place, and should all be tried. But "no scheme will succeed", said Prof. ALAN MONCRIEFF, "unless the hospital boards and their medical advisers appreciate the importance of our doctors working abroad"; to which Mr. N. M. AGNEW, as chairman of one of the boards, retorted that if anybody needs educating it is the medical profession. The truth of this is all too plain from the shocking story told in the Personal Paper on p. 778.

1. Birth of Nigeria's University. By KENNETH MELLANBY, C.B.E., SC.D. London: Methuen. 1958. Pp. 263. 25s.

2. Dialogues of Today, *Lancet*, Jan. 24, 1959, p. 195.
3. *ibid* 1958, ii, 1111.
4. Wells, C. A. *Times*, March 16, 1959; see also letters by Prof. K. Hill (March 19), Prof. E. C. Mekie (March 23), Prof. Milnes Walker (April 1), and Prof. F. Heath (April 7).

Chlorothiazide

FOR many years the supremacy of the organic mercurial compounds for the removal of œdema fluid was never seriously disputed. They are potent, reasonably safe (except intravenously), and remarkably well tolerated. But usually they must be given by intramuscular or subcutaneous injection, and unpleasantly large doses of ammonium chloride are needed for the full diuretic effect. Furthermore, renal tubular damage is a hazard; the nephrotic syndrome develops occasionally,[1] and urinary casts, leucocytes, and erythrocytes increase temporarily after mersalyl injections. Hitherto oral diuretics which do not contain mercury have proved disappointing. Acetazolamide increases urinary excretion of sodium bicarbonate by inhibiting renal carbonic anhydrase; but diuresis by this means is short-lived and self-limiting because the metabolic acidosis which the drug itself produces prevents any further sodium loss.[2–4] The aminouracil compounds, aminometradine and amisometradine, increase the urinary output of chloride and sodium moderately [5]; but the diuresis is slow, the drugs tend to accumulate in the body, and with aminometradine gastrointestinal symptoms are common. Chlorothiazide is the latest non-mercurial diuretic which is effective when given by mouth. Since it was generally introduced at the beginning of last year, many reports of its use in cardiac, hepatic, and renal œdema,[6–13] toxæmia of pregnancy,[14 15] and premenstrual œdema [8 16] have testified to its potency, rapid action, and relative lack of toxicity.

Chemically, chlorothiazide is a substituted 1,3-benzene disulphonamide (6 - chloro - 7 - sulphamyl - 1,2,4-benzothiadiazine-1,1-dioxide). One sulphonamide group is free, whereas the other is linked with an acyl-amino group (opposite the free sulphonamide group on the benzene nucleus) forming a benzothiadiazine ring. The formula was elaborated by NOVELLO and SPRAGUE [17] following the discovery by BEYER et al.[18] that certain derivatives of benzene-1,3-disulphonamides, although potent inhibitors of carbonic anhydrase in vitro, promote the urinary excretion of chloride in the living animal. The maximum effective dose of chlorothiazide is 2 g.; this is usually equivalent to 2 ml. mersalyl by intramuscular injection. The drug is rapidly absorbed from the gastrointestinal tract, and the rate of urine flow increases within two hours, continuing above control values for about twelve hours.[13 19] Experimentally BEYER [20] has shown that chlorothiazide is probably confined to the extracellular-fluid space, and unlike acetazolamide it is not preferentially concentrated in erythrocytes. The drug is rapidly excreted in the urine (from which it can be recrystallised in a chemically pure form) in amounts which suggest that it is removed from the circulation both by glomerular filtration and by tubular secretion, the renal clearance approaching that of *p*-aminohippuric acid. Tubular secretion of both drugs can be reduced by probenecid, which implies that they are handled similarly by the tubules; but chlorothiazide may *raise* the serum-uric-acid level.[6 12] In contrast to organic mercurials, the diuretic response to chlorothiazide is not influenced by changes of acid-base balance.[20] Ammonium chloride does not potentiate its action, and the development of hypochloræmia does not inhibit its effect. Patients resistant to mercurial drugs sometimes respond temporarily to chlorothiazide [6 8]; and, when either drug alone is ineffective, diuresis may be obtained by combining them.[6 8 9]

In most patients the predominant effect of chlorothiazide is to increase the urinary excretion of chloride and sodium in roughly equimolar amounts. This resembles the effect of mercury, and it means that proportionately more chloride than sodium is lost from the extracellular fluid, where the concentration of chloride is only just over two-thirds that of sodium. Consequently, serum-chloride levels fall to a greater extent than serum-sodium levels, and the "low-salt syndrome" with low serum levels of both sodium and chloride easily develops.[12] Chlorothiazide also causes a considerable loss of potassium in the urine, particularly in patients with severe fluid retention. In fact the increased excretion of chloride ions is accompanied by loss of sodium and potassium ions in varying ratios which depend chiefly on the nature and extent of the disease and on the sodium content of the diet. Some patients with ascites due to liver disease lose potassium instead of sodium,[21] and a similar effect has been observed in 2 children with nephrosis.[6] Some depletion of potassium is therefore almost inevitable; and serum-potassium levels may fall considerably.[6–9 12 13] Loss of potassium from the body-cells is an integral part of the biochemical disturbance in patients seriously ill with cardiac or hepatic disease, so the potassium-losing effect of chlorothiazide is particularly deleterious in these patients. Usually it does not produce any definite symptoms,[6–9] except, perhaps, slight lethargy and muscular weakness. But hypokalæmia may precipitate hepatic coma in patients with cirrhosis of the liver [21]; muscular weakness will further impede ventilation in patients with respiratory failure and cor pulmonale; the toxic effects of digitalis are enhanced by low serum levels of potassium [22]; and potassium depletion is well-known to produce renal tubular damage.[23] Oral potas-

1. Riddle, M., Gardner, F., Beswick, I., Filshie, I. *Brit. med. J.* 1958, i, 1274.
2. Hanley, T., Platts, M. M. *Lancet*, 1956, i, 357.
3. Counihan, T. B., Evans, B. M., Milne, M. D. *Clin. Sci.* 1954, **13**, 583.
4. *Lancet*, 1955, i, 706.
5. Platts, M. M., Hanley, T. *Brit. med. J.* 1956, i, 1078.
6. Laragh, J. H., Heinemann, H. O., Demartini, F. E. *J. Amer. med. Ass.* 1958, **166**, 145.
7. Goodkind, M. J., Harvey, R. M., Richards, D. W. *Amer. J. med. Sci.* 1958, **235**, 164.
8. Bayliss, R. I. S., Marrack, D., Pirkis, J., Rees, J. R., Zilva, J. F. *Lancet*, 1958, i, 120.
9. Slater, J. D. H., Nabarro, J. D. N. *ibid.* p. 124.
10. Watson, W. C., Thomson, T. J., Buchanan, J. M. *ibid.* p. 1199.
11. Myerson, R. M., Stout, R. E., Forte, A. L. *New Engl. J. Med.* 1959, **260**, 280.
12. Dinon, L. R., Kim, Y. S., Vander Veer, J. B. *Amer. J. med. Sci.* 1958, **236**, 533.
13. Ford, R. V., Rochelle, J. B., Handley, C. A., Moyer, J. H., Spurr, C. L. *J. Amer. med. Ass.* 1958, **166**, 129.
14. Finnerty, F. A., Buchholz, J. H., Tuckman, J. *ibid.* p. 141.
15. Assali, N. S., Judd, L. L., Mondz, N. *ibid.* 1959, **169**, 26.
16. Bickers, W. *Virginia med. Mon.* 1958, **85**, 613.
17. Novello, F. C., Sprague, J. M. *J. Amer. chem. Soc.* 1957, **79**, 2028.
18. Baer, J. E., Leidy, L., Brooks, A. V. *Fed. Proc.* 1957, **16**, 278. Beyer, K. H., Baer, J. E., Russo, H. F., Haimbach, A. S. *ibid.* p. 282. Russo, H. F., Baer, J. E., Noll, R. M., Beyer, K. H. *ibid.* p. 333.
19. Matheson, N. A., Morgan, T. N. *Lancet*, 1958, i, 1195.
20. Beyer, K. H. *Ann. N.Y. Acad. Sci.* 1958, **71**, 363.
21. Read, A. E., Haslam, R. W., Laidlaw, J., Sherlock, S. *Brit. med. J.* 1958, i, 963.
22. Lown, B., Salzberg, H., Enselberg, C. D., Weston, R. E. *Proc. Soc. exp. Biol., N.Y.* 1951, **76**, 797.
23. Relman, A. S., Schwartz, W. B. *Amer. J. Med.* 1958, **24**, 764.

sium supplements are therefore essential during treatment with chlorothiazide. Potassium chloride 3–6 g. daily is the most suitable; but potassium salts often cause unpleasant symptoms, particularly in ill patients,[24] and making out a prescription does not guarantee that the tablets will be taken. Therefore the dose of chlorothiazide should be kept to a minimum by giving intermittent courses of the drug (e.g., for three days of the week) together with a low-sodium diet rich in potassium. Even these safeguards are sometimes inadequate,[9] and it is wise to check the serum-potassium level regularly. Osmotic diuresis is always associated with some increase of potassium excretion, but the particular liability of chlorothiazide to cause potassium depletion is probably connected with the fact that it inhibits carbonic anhydrase. This can be demonstrated easily in vitro, but in vivo it is overshadowed by the rapid increase in the rate of chloride excretion, which is unlike the renal response to carbonic-anhydrase inhibition. As a result, hypochloræmia with a raised serum-bicarbonate level (also partly due to hypokalæmia) tends to develop, contrasting with the hyperchloræmic acidosis induced by acetazolamide. Nevertheless, in acute experiments chlorothiazide does increase the rate of bicarbonate excretion by the kidneys and it lowers the secretion-rate of hydrogen ions [13 15 19]; the urine becomes alkaline, and SLATER and NABARRO [9] have observed a transient slight decrease of the pH of the arterial blood after a 3 g. oral dose of chlorothiazide. This implies inhibition of renal carbonic anhydrase in vivo, which is well known to increase the rate of potassium excretion by the kidneys.[25]

How chlorothiazide increases the rate of urinary chloride excretion is also poorly understood, but the mechanism is probably different from that of mercurial diuretics. Chlorothiazide does not produce any detectable change of the glomerular filtration-rate either in man [14 15] or in the dog,[20 26] so tubular resorption is presumably reduced. LARAGH et al.[6] have shown that, in contrast to meralluride, the free water clearance during mannitol diuresis is not increased—i.e., for a given solute output chlorothiazide produces a more concentrated urine than meralluride. This indicates that chlorothiazide acts further down the tubule than mercury. The experiments of PITTS [26] in dogs provide supporting evidence. He found that when a maximal renal response to chlorothiazide is produced, mercury (as chlormerodrin) in maximal effective doses will increase sodium and chloride excretion still further. Reversing the order by giving chlormerodrin first had the same effect.

In common with other diuretics, chlorothiazide has a mild but definite hypotensive effect in some non-œdematous patients with increased arterial tension.[27–29] Of greater importance is the fact that the hypotensive effect of antihypertensive drugs and sympathectomy is considerably increased.[27 30] Because chlorothiazide apparently can be given continuously for long periods without loss of effectiveness, the dose of antihypertensive compounds must be reduced during chlorothiazide treatment and the dangers and unpleasant side-effects of these drugs will be correspondingly diminished. In the treatment of severe hypertension FREIS [31] finds that, with the addition of chlorothiazide 0·5 g. twice daily, the dose of ganglion-blocking drugs can be reduced by about half. This amount of chlorothiazide usually produces hypokalæmia, and the advantages of chlorothiazide therapy must be balanced against the dangers of potassium depletion. The way in which chlorothiazide reduces the blood-pressure is undecided. WILSON and FREIS [32] and TAPIA et al.[30] have observed that chlorothiazide produces a reduction in plasma-volume which corresponds in time to the increased sodium output and the fall in blood-pressure. But other workers claim that the hypotensive effect does not depend on sodium depletion [28] or on reduced cardiac output.[33]

Apart from the metabolic consequences of giving such a potent diuretic, chlorothiazide is remarkably well tolerated. Nausea, anorexia, skin rashes, and generalised sensitivity reactions [12] develop occasionally —probably about as often as with other sulphonamides. For the same reason depression of the bone-marrow is to be expected in a small proportion of patients. It is too early to say how commonly this is likely to happen; but already a fatal case of bone-marrow dysplasia is on record,[34] and 6 cases of thrombocytopenic purpura developing during chlorothiazide treatment have been reported.[35] Bearing in mind the large number of patients who are receiving the drug, this probably represents a low incidence.

Chlorothiazide is a most powerful diuretic, and because it is so easily administered the greatest care must be taken to avoid overdosage. Mercurial diuretics, since they do not usually cause hypokalæmia, remain the safest means of removing the œdema of patients seriously ill with hepatic or cardiac disease. But for the treatment of renal œdema, whether due to nephrosis or toxæmia of pregnancy, chlorothiazide is clearly invaluable, and outside hospital it has made the relief of mild œdema of all types more pleasant. Modifications of the chlorothiazide molecule in attempts to separate the mersalyl-like action from the potassium-losing effect are being developed. Already 3,4-dihydrochlorothiazide and its 6-trifluoromethyl derivative are on the market. Judged by their diuretic effect both drugs are about 10–20 times as potent as chlorothiazide [36 37]; but this in itself is no virtue, and it is too early to say whether they are any less likely to produce an excessive loss of potassium. Present evidence suggests that this is not so.[37 38]

24. Flear, C. T. G., Hill, M., Thomas, G. *Lancet*, 1956, ii, 1190.
25. Berliner, R. W., Kennedy, T. J., Orloff, J. *Amer. J. Med.* 1951, **11**, 274.
26. Pitts, R. F. *ibid.* 1958, **24**, 745.
27. Freis, E. D., Wanko, A., Wilson, I. M., Parrish, A. E. *J. Amer. med. Ass.* 1958, **166**, 137.
28. Hollander, W., Wilkins, R. W. *Boston med. Quart.* 1957, **8**, 69.
29. Hall, R., Owen, S. G. *Lancet*, Jan. 17, 1959, p. 129.
30. Tapia, F. A., Dustan, H., Schneckloth, R. A., Corcoran, A. C., Page, I. H. *ibid.* 1957, ii, 831.
31. Freis, E. D. *J. Amer. med. Ass.* 1959, **169**, 105.
32. Wilson, I. M., Freis, E. D. *Circulation*, 1958, **18**, 800.
33. Alexandrow, D., Wysznacka, W., Gajewski, J. *New Engl. J. Med.* 1959, **260**, 51.
34. Zuckerman, A. J., Chazan, A. A. *Brit. med. J.* 1958, ii, 1338.
35. Nordqvist, P., Cramér, G., Björntorp, P. *Lancet*, Feb. 7, 1959, p. 271.
36. Richterich, R. *Experientia*, 1958, **14**, 458.
37. Sele, V. *Ugeskr. Læg.* 1958, **120**, 1592.
38. Esch, A. F., Wilson, I. M., Freis, E. D. *Med. Ann. D.C.* 1959, **28**, 9.

Prolonged Pregnancy

DESPITE continued interest in prolonged pregnancy,[1–5] there is still nothing like unanimity on its management. RACKER et al.[6] regarded surgical induction as so safe that they undertook it in every case where labour had not begun at term. But induction still has dangers[7]: GIBSON[8] reported intrauterine death in 25% of cases where labour was delayed for more than 72 hours after artificial rupture of the membranes; and COPE and PEARSON[9] found that, of 999 cases in which surgical induction was undertaken on account of varied indications, subsequent cæsarean section was necessary in 145 (14%). Statistical study of large numbers of cases in which the results of routine induction were compared with those of non-interference have shown no clear advantage one way or the other[1]; but some improvement in fœtal survival-rate has been reported from reserving induction for women with prolonged pregnancies who are exposed to special risk—for instance, older women and women with hypertension. In our own columns the divergence of opinion has been made clear. GIBBERD,[2] impressed by the imperfection of present methods of induction, declared that it was probably better not to engage at all in the treatment of postmaturity than to embark on a rigid policy of prevention. WRIGLEY[10] suggested that if at the expected date of confinement the patient seemed to be in perfect health and the fœtus small, the case should be watched (an exception was the elderly primigravida, for whom labour should be induced); if the fœtus seemed normal the case should be watched, though probably not for so long; but if the fœtus appeared without doubt to be large, labour should be induced. This view has been challenged by THEOBALD,[3] who finds that a more vigorous policy of intervention is associated with a perinatal mortality of about 0·5%.

Prolongation of pregnancy increases the risk to the fœtus in two ways. First, owing to continued growth and hardening of the head, mechanical difficulties may arise; in a high proportion of lengthy labours with disorderly uterine activity the fœtus is large and postmature. Secondly, the fœtus may be damaged directly by injury during birth, or may become anoxic either during abnormal labour or before labour owing to its oxygen requirements outstripping the placental reserve. Unhappily, estimates of the placental reserve are rarely better than guesses; and this, combined with the absence of a fully safe and sure method of inducing labour, places the obstetrician who opts for attempted induction in the tactically unsound position of recommending treatment involving risk in order to avoid danger that may not exist. If active interference is limited to special-risk cases in which there is good reason to believe harm may shortly come to the fœtus, then the occasional cæsarean section where attempted induction has failed will be justified; but it is not so satisfactory to have to deliver the healthy young primigravida in this way merely because pregnancy has passed term and attempted induction has proved unsuccessful. The decision whether to interfere or not is often dictated largely by assessment of fœtal size, and this is an unsatisfactory guide to maturity. Where the fœtus grows at less than the normal rate and the placenta is also small, the obstetrician may erroneously judge that there has been an "error in dates" and allow pregnancy to continue too long. In some such cases the fœtus will die in utero; and at birth the placenta is found to be tiny and often grossly infarcted. In other cases fœtus and placenta are simply slow in maturing and a healthy child may be born well after term. Practically the only physical sign of "postmaturity" is obtained by palpation, when, owing to absorption of liquor amnii, the fœtus seems to fill the uterus.

WALKER'S[11] work on oxygen saturation of fœtal-cord blood showed falling levels in the primigravida over 25 years of age when pregnancy was prolonged beyond the 41st week. Low levels were found when pregnancy was complicated even in the young, regardless of parity. WALKER found that the main anoxia-producing hazards included pre-eclampsia, hypertension, increasing maternal age (especially in the primigravida), and previous "unexplained" stillbirth or neonatal death. Other studies of oxygen saturation, using spectrophotometric techniques,[12] have not confirmed these findings; no tendency towards fall in levels was found in the older primigravida nor with advancing fœtal age. But investigations of placental and uterine blood-flow by clearance-rates of radioactive sodium[13 14] suggest defects most significant with prolonged pregnancy, especially when complicated by pre-eclampsia. A totally different approach to study of placental function—by quantitative estimation of pregnanediol excretion[15]—has revealed excretion levels below the normal average in hypertension and pre-eclampsia, though detailed examination of pregnancies prolonged beyond term has not yet been reported. SHEARMAN[16] has confirmed that excretion of pregnanediol is significantly lower in pre-eclampsia.

Further investigation is needed to establish the facts about placental function after term. Clinically there is need for a reliable guide to placental reserve before labour begins; at present only radioactive-isotope and hormone-excretion studies offer any hope of meeting this need. Until more is learnt about the physiology of labour—and especially about the causes of its onset—safer and surer methods of induction are unlikely to be found.

1. Browne, F. J. *Brit. med. J.* 1957, i, 851.
2. Gibberd, G. F. *Lancet*, 1958, i, 64.
3. Theobald, G. W. *ibid.* Jan. 10, 1959, p. 59.
4. Walker, J. *Amer. J. Obstet. Gynec.* 1958, **76**, 1231.
5. Cope, I. *Med. J. Aust.* 1959, i, 196.
6. Racker, D., Burgess, G. H., Manly, G. *Lancet*, 1953, ii, 953.
7. Parker, R. B. *J. Obstet. Gynæc. Brit. Emp.* 1957, **64**, 94.
8. Gibson, G. B. *ibid.* 1952, **59**, 814.
9. Cope, I., Pearson, M. G. *Brit. med. J.* 1958, i, 1211.
10. Wrigley, A. J. *Lancet*, 1958, i, 1167.
11. Walker, J. *J. Obstet. Gynæc. Brit. Emp.* 1954, **61**, 162.
12. Bancroft-Livingstone, G., Neill, D. W. *ibid.* 1957, **64**, 498.
13. Browne, J. C. McC., Veall, N. *ibid.* 1953, **60**, 141.
14. Moore, P. T., Myerscough, P. R. *ibid.* 1957, **64**, 207.
15. Russell, C. S., Paine, C. G., Coyle, M. G., Dewhurst, C. J. *ibid.* 1957, **64**, 649.
16. Shearman, R. P. *ibid.* 1959, **66**, 1.

Annotations

PROFOUND HYPOTHERMIA IN CARDIAC SURGERY

IN two papers which we publish this week Mr. Drew and his colleagues describe a method for operating on the empty heart while maintaining the viability of other organs. The combination of hypothermia with extracorporeal circulation has interested many workers in the past few years.[1-4] The main attraction is that reduction, by means of hypothermia, of the organism's total oxygen requirements reduces the need for a heart-lung machine capable of delivering high outputs of oxygenated blood. Accordingly the design of the machine can be simplified, and much less donor blood is needed to prime the extracorporeal circulation. Drew et al. have employed this method, but have taken a step forward by reducing the temperature much further and using the patient's own lungs for their normal function of oxygenation. The simplified circuit omits the artificial oxygenator and comprises two blood pumps (one pump to bypass each ventricle), a heat exchanger, tubing, and reservoirs. Once the temperature has been reduced to about 15°C, the pump circulations can be stopped and the surgeon has forty-five minutes to operate on the empty heart without any serious risk.

Provided that the circulation through the lungs can be maintained at normal pressures, the theoretical advantage is considerable. Drew's findings in laboratory animals and in patients of relative freedom from postoperative lung troubles is encouraging; but his experimental and clinical series so far are small, and it would be interesting to have data on the pulmonary arterial and venous pressures. Drew and his fellow-workers have shown that in their hands this technique is successful; but it must be emphasised that they are a highly skilled team, and at present it would be unrealistic to compare their technique with established techniques of heart-lung bypass under normothermic conditions.

The pumps in these experiments contribute greatly to the cooling, and even more to the rewarming, as well as maintaining the circulation when the heart fails; but, as Drew et al. point out, the optimum flow of blood per kilogramme body-weight required at low temperatures is still unknown. Their technique, by requiring the pump only during the period of cooling and rewarming and not during the period of cardiotomy, keeps the time for using the heart bypass down to a reasonable period; and so there has been no hæmolysis. The operation itself seems to be fairly straightforward provided that the left atrium can be successfully drained; but the method has not yet been tried in some circumstances, such as the complete correction of the tetrad of Fallot with a hypoplastic pulmonary artery and infundibular or pulmonary valvular stenosis.

Because the circulation ceases completely during the period of intracardiac surgery, a cannula that is in the way during this time can be withdrawn; and in one case a pulmonary-artery cannula was in fact withdrawn. Owing to the relative simplicity of the extracorporeal circuit combined with the hypothermia, the dose of heparin does not need to be as great as that normally used in heart-lung bypass procedures. This should help to lessen postoperative bleeding.

With the present rapid increase of centres starting to use extracorporeal circulation for intracardiac surgery, the demands on regional blood-banks are rising alarmingly; and the method of Drew et al., with its relatively small requirement of 2–3 pints of blood for priming the apparatus, may help to resolve this difficulty.

Hypothermia at still lower temperatures is, as Drew et al. suggest, an attractive idea whose practicability is supported by some experimental evidence.[5-7] But it would be premature to suggest that the technique that has now been developed will replace others. Nor at the moment does it make surgery any easier; and the need for a highly skilled team, both for the operation and for postoperative care, is probably no less great than it is with a normothermic heart-lung bypass. On the other hand, we are still far from finality in the techniques of cardiac surgery; and we hope that the theoretical advantages of the Westminster method will be fully realised in practice. Mr. Drew and his colleagues can be congratulated on an original approach, and we look forward to further news of its application.

HÆMADSORPTION VIRUSES

MANY new developments in cultivating viruses are being reported at present. Eighteen months ago Vogel and Shelokov [8] described a rapid method for isolating and identifying influenza viruses. The virus was isolated in monkey-kidney-tissue cultures, and after an incubation period red blood-cells were added to the culture tubes. The red blood-cells adhered to the infected monkey-kidney cells, and this hæmadsorption (as it is now called) was used to identify the virus. Chanock et al.,[9] experimenting with this method, isolated from children with acute respiratory disease two new viruses which had not been recognised before. On first isolation, these hæmadsorption viruses types 1 and 2 showed no cytopathic effect on the monkey-kidney cells, so their recognition depended entirely on the isolation technique which had been used. The hæmadsorption viruses share many biological affinities with the influenza viruses, and the type-2 virus was found to be related antigenically to the Sendai virus (at one time known as influenza D).

Now Chanock et al.[10] describe a systematic attempt to isolate hæmadsorption viruses from 1738 infants and children in three Washington, D.C., hospitals. The study population was made up of infants and children brought to outpatient clinics or for admission to hospital, with various respiratory illnesses, while a control group consisted of a similar number of children without respiratory illness and matched with the study group according to age, sex, and socioeconomic background. The respiratory illnesses studied—croup, bronchiolitis, pharyngitis, or pneumonia—did not seem to be caused primarily by bacteria. From each child a throat swab was taken on admission to hospital or at the first clinic visit, and virus isolation was attempted by the technique of Vogel and Shelokov.[8]

1. King, H., Chien Sheng Su, Bounos, G., Hardin, R., Derin, F., Shumacher, H. B. Extracorporeal Circulation; p. 193. Springfield, Ill., 1958.
2. Sealy, W. C., Brown, I. W., Young, G. W., Stephen, R. C., Harris, J. S., Merritt, D. *Surg. Gynec. Obstet.* 1957, **104**, 441.
3. Sealy, W. C., Brown, I. W., Young, W. G. *Ann. Surg.* 1958, **147**, 603.
4. Gollan, F., Hamilton, E. C., Meneely, G. R. *Surgery*, 1954, **35**, 88.
5. Andjus, R. K. *J. Physiol.* 1955, **128**, 547.
6. Smith, A. *Proc. roy. Soc.* B, 1957, **147**, 533.
7. Lewis, F. J. Physiology of Induced Hypothermia; p. 143. Washington, 1956.
8. Vogel, J., Shelokov, A. *Science*, 1957, **126**, 358.
9. Chanock, R. M., Parrott, R. H., Cook, K., Andrews, B. E., Bell, J. A., Reichelderfer, T., Kapikian, A. Z., Mastrota, F. M., Huebner, R. J. *New Engl. J. Med.* 1958, **258**, 207.
10. Chanock, R. M., Vargosko, A., Luckey, A., Cook, M. K., Kapikian, A. Z., Reichelderfer, T., Parrott, R. H. *J. Amer. med. Ass.* 1959, **169**, 548.

Type-1 hæmadsorption virus was isolated twenty times more commonly from patients with respiratory illness than from the controls, and altogether 2·3% of the respiratory illnesses yielded type-1 virus. 3·9% of the respiratory illnesses yielded type-2 virus, and this incidence was thirty-four times greater than that in the controls. The results of limited serological studies supported the findings of virus isolations. Isolations of type-1 virus seem to have been associated to about the same degree with pneumonia, croup, bronchiolitis, pharyngitis, or mild respiratory disease. Type-2 virus was recovered from patients with croup, pharyngitis, or mild illness; but the recovery-rate from individuals with croup—16·7%—was significantly higher than that for other respiratory viruses.

These findings suggest a causal association between virus isolations and clinical illness, and their significance is strengthened by studies carried out by Reichelderfer et al.[11] of the results of inoculating 32 men with the type-2 virus. These men had virus swabbed on the pharynx and lower palpebral conjunctiva and sprayed and instilled into the nose and pharynx. On the fifth day after inoculation they showed no illness, and they were then released from isolation. On the sixth day, however, 6 men complained of respiratory illness, and when the others were examined many were found to show clinical signs. The most common illness was a mild " cold-like " infection with nasal obstruction and discharge, coughing, and sneezing and with recovery in two to three days. Altogether 18 of the 32 men showed clinical illness, and in 4 (1 of whom had no other evidence of infection) fever of 100–101°F developed.

The evidence seems clear, therefore, that the hæmadsorption viruses should be accepted into the fast-growing collection of viruses responsible for respiratory disease in man. Like other respiratory viruses, the hæmadsorption viruses can cause mischief at different anatomical sites in the respiratory tract, and the total damage they cause varies from a mild cold to croup or pneumonia. These viruses are being studied at present at the Medical Research Council's Common Cold Research Unit in Salisbury, and their isolation in this country has been reported.[12] It will be important to learn what proportion of the huge volume of upper-respiratory illnesses in this country is due to these viruses.

INJURIES OF THE CERVICAL SPINE

THE great flexibility of the cervical spine protects it somewhat from fractures and dislocations. But these have become commoner, owing to an increase in automobile accidents at high speeds. In a collision the cervical spine may be damaged by the compression forces transmitted to it when the head strikes a windscreen or car roof, or, more often, by the severe hyperextension, sometimes followed by acute flexion, that accompany sudden deceleration—movements that are liable to give rise to " whiplash injury ", in which neurological symptoms may be associated with no evident damage to bones or joints.[13]

The management of fractures and dislocations of the neck poses three major problems: the reduction of any skeletal deformity; the retention of the corrected position; and the conservation or restoration of cervical-cord function. It is now generally agreed that bony deformity, whether associated with a neurological lesion or not, is best reduced by cranial traction.[14 15] Crutchfield, whose advocacy established this method of treatment, recommended an initial application, by skull tongs, of up to 35 lb. weight. When reduction had been effected the weight was reduced to 5–6 lb., and this was maintained for six weeks or longer to guard against recurrent displacement of the damaged vertebræ. Traction is indisputably efficacious, and it is wise—in view of possible disc retropulsion—to apply skull tractors to every patient who is quadriplegic after an accident, even if radiographs show no gross skeletal deformity. But Rogers [16] has shown that displacement may recur after lengthy traction immobilisation is discontinued. Such secondary deformity is especially likely when gross instability is manifested by easy initial correction; and prolonging traction in such cases may increase the liability to late subluxation by stretching those ligaments which are still intact.

Robinson [17] has therefore urged a wider use of internal fixation, whether the spinal cord is intact or damaged; and Forsyth et al.[18] have reported 38 cases treated by early spinal fusion. This operation, which is not severe, can usually be performed within one or two weeks of injury. The spinous processes of the damaged vertebra and of that above and that below it are exposed and wired together. The laminæ are bared by subperiosteal stripping, and thin " matchstick ' bone grafts are laid across them. Decortication of the laminæ is not necessary, and bank bone will serve no less well than that taken from the patient. Gentle traction is applied until the wound has healed, when the patient may get up in a light brace. Forsyth et al. found that the eventual deformity was less, recurrent symptoms were fewer, and the period in hospital was shorter than in a similar number of patients treated conservatively.

Spinal fusion must, of course, not be performed until any question of a laminectomy has been ruled out. (Likewise any extensive resection of the neural arch complicates a subsequent fusion operation, but does not exclude it since well-tried techniques exist for fusing vertebral bodies and posterior articulations.) The indications for exploring the cord after cervical injuries are few. No paraplegic who was completely paralysed immediately after injury, and whose condition has not been improved by correction of any skeletal malaligment, will be helped by laminectomy, whether a manometric block is demonstrable or not.[15] But in those rare instances where paralysis is progressive, exploration is indicated; and a case can be made for inspecting an incomplete lesion. But the operation should be carried out by a skilled surgeon, and with the patient in traction; for any manipulation of a displaced and compromised spinal cord may have a reverse effect to that intended.

Finally, some patients, left with grave paralysis, insist on " having the cord examined ". These people face a severe disability over which they may brood to the end of their days; and, when they persist in their request after the limitations of surgery have been fully explained, most surgeons would consider it unreasonable to refuse to undertake at least a limited laminectomy.

11. Reichelderfer, T. E., Chanock, R. M., Craighead, J. E., Huebner, R. J., Turner, H. C., James, W. *Science*, 1958, **128**, 779.
12. Sutton, R. N. P., Clarke, S., Tyrrell, D. A. J. *Lancet*, Feb. 21, 1959, p. 395.
13. See *Lancet*, Jan. 24, 1959, p. 188.
14. Holdsworth, F. W. Modern Trends in Orthopædics; p. 199. London, 1956.
15. Kahn, E. A. *J. Bone Jt Surg.* 1959, **41A**, 8.
16. Rogers, W. A. J. *ibid.* 1957, **39A**, 341.
17. Robinson, R. A. *ibid.* 1959, **41A**, 3.
18. Forsyth F. Davis .C. ,Alexander ,E. Underal, R. *ibid.* 1959, **41A**, 17.

PENICILLIN V FOR PNEUMONIA

EARLY trials of oral penicillin therapy proved disappointing because the preparations then available—penicillin G (benzylpenicillin) and its derivatives—are readily destroyed by acid gastric juice; hence, except in children and old people, blood-levels were very erratic.[1] Interest in oral penicillin therapy languished, therefore, until Austrian workers[2,3] discovered that penicillin V (phenoxymethylpenicillin) was stable in acid media, and thus survived the passage through the stomach to the intestine. Successful results have since been claimed for oral therapy with penicillin V in various conditions including dental sepsis,[4] pneumonia and other respiratory infections,[5–7] streptococcal infections in children,[8] staphylococcal sepsis,[9] and subacute bacterial endocarditis[10,11]; and the drug has now been widely used on the Continent for some years. No doubt because of previous unsatisfactory experience with oral therapy, penicillin V has been regarded with more circumspection in this country, and a report of its use in pneumococcal pneumonia by Reeves et al.[12] is therefore welcome.

In 1956–57 they treated 68 patients aged 14 to 80 years with penicillin V alone. 43 (63%) of the patients were moderately ill and 25 (37%) severely ill; mild cases were excluded from the trial. 59 patients (87%) responded excellently, showing much clinical improvement and lysis of fever within twenty-four hours. None of these patients was "critically" ill, but 17 were severely ill and 26 had concomitant disease. 6 patients (9%) responded satisfactorily though less promptly; but 1 of these had bacteræmia and 4 had severe complicating disease. The outcome was unsatisfactory in 3 cases: 2 patients died, and the 3rd developed pericarditis and empyema but eventually recovered. The patients who died were elderly and so debilitated by chronic disease that it appeared unlikely that they would have survived with any form of penicillin treatment. Results in this series were in keeping with those of a similar study of penicillin V in 42 patients with pneumococcal pneumonia carried out in the previous year at the same hospital.[6] Of the total of 110 patients treated in the two years 104 (95%) responded satisfactorily, and only 6 (5%) did not.

From their own and other experience Reeves et al. seem justified in claiming that oral therapy with penicillin V is adequate for the majority of respiratory infections caused by penicillin-sensitive organisms; for absorption of the drug from the intestine appears to be regular,[13–16] although not complete (only about 30% of a dose is excreted in the urine compared with about 80% of a dose of parenteral penicillin[13]). In severe cases, however, where high blood-levels of penicillin are urgently required, parenteral penicillin therapy is necessary; and some prefer to start treatment in all cases with parenteral penicillin and continue with penicillin V. 60 mg. of penicillin V is reckoned to be equivalent to 100,000 units of parenteral penicillin G, and the usual dosage schedule for adults is 240 mg. four-hourly with a double dose before retiral to rest. 120 mg. four-hourly is suitable for children, and 60 mg. four-hourly for infants. There is, however, still no unanimity about dosage; some think that half the dosages mentioned are sufficient, and Reeves et al. used 250 mg. six-hourly for adults. It has been claimed that higher blood-levels are achieved if the drug is given about half an hour after food.[17,18] Gastrointestinal upset appears to be uncommon, although diarrhœa, if it occurs, may be severe. On the other hand penicillin-V therapy is convenient in domiciliary practice; it saves nurses' time in hospital; it avoids the risk of needle-transferred hepatitis, and it spares patients the pain of injections. Moreover, although sensitisation may develop, it seems to be rarer and less severe than with parenteral therapy; and patients sensitive to parenteral penicillin are not necessarily sensitive to penicillin V.

Evidence of the efficacy of penicillin-V treatment continues to accumulate, and in view of the manifest advantages of oral therapy this must be regarded as a significant advance.

1. Fairbrother, R. W., Daber, K. S. *Lancet*, 1954, i, 858.
2. Brunner, R. *Öst. chem. Ztg*, 1953, **54**, 138.
3. Brandl, E., Margreiter, H. *ibid.* 1954, **55**, 11.
4. Hermann, H. *Dtsch. ZahnärztBl.* 1955, **9**, 360.
5. Hart, F. D., Burley, D., Manley, R., Brown, G. *Brit. med. J.* 1956, i, 496.
6. McWhorter, H. B., Walker, W. F., Henry. R. B., Jr., Hamburger, M. *Antibiot. Ann.* 1956 57, p. 300.
7. Lamb, R., Maclean, E. *Brit. med. J.* 1957, ii, 191.
8. Breese, B. B., Disney, F. A. *Amer. J. Dis. Child.* 1956, **92**, 20.
9. Burn, J. I., Curwen, M. P., Huntsman, R. G., Shooter, R. A. *Brit. med. J.* 1957, ii, 193.
10. Quin, E. L., Colville, J. M., Cox, F., Truant, J. *J. Amer. med. Ass.* 1956, **160**, 931.
11. Sandler, G., Parish, P. A. *Brit. med. J.* 1958, i, 377.
12. Reeves, J. T., Garfield, J., Polasky, N., Hamburger, M. *Arch. intern. Med.* 1959, **103**, 173.
13. Henry, L., White, G., Meynell, M. J. *Brit. med. J.* 1957, i, 17.
14. Wright, W. W., Krishbaum, A., Arret, B., Putnam, L. E., Welch, H. *Antibiot. Med.* 1955, **1**, 490.
15. Martin, W. J., Nichols, D. R., Heilman, F. R. *Proc. Mayo Clin.* 1955, **30**, 467.
16. Rinsler, M. G., Cunliffe, A. C. *Lancet*, 1956, ii, 328.
17. Jones, W. F., Finland, M. *New Engl. J. Med.* 1955, **253**, 754.
18. Holborow, E. J., Bywaters, E. G. L., Johnson, G. D. *Brit. med. J.* 1956, ii, 1355.

THE BUDGET

IN outlining his Budget last Tuesday Mr. Heathcoat Amory accepted the definition of our financial position as "a springtime of opportunity and not a harvest of prosperity". The proposed reduction in the standard rate of income-tax by ninepence in the pound, and of the three lower rates by sixpence, favours the comparatively well-to-do, as also do the cuts by a sixth in the purchase-tax on articles now taxed at 60%, 30%, and 15% (the 5% tax is to remain unchanged). In other words the greatest relief is in the tax on near-luxury goods; and the ordinary housewife will find that she is little better placed than before to fill her weekly shopping-basket. The changes in the post-war credit arrangements, by which the neediest and the blind will receive immediate repayment, and others earlier repayment and meanwhile interest at $2\frac{1}{2}$%, go some way towards ending an indefensible anomaly. Wage-earners will be cheered by the Chancellor's announcement that near-price-stability has been achieved. His promise of early additional help to public-service pensioners is also welcome, but to the needy old-age pensioner he seems to offer virtually nothing. This Budget may achieve the Chancellor's aims of increasing production and lowering unemployment; but to many it may seem that he has not made the most of a possibly unique opportunity to aid those whose need is greatest.

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Public Health

TRENDS IN HOME NURSING

The Birmingham Service 1950–57

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THE rapid advance in medical knowledge and the administrative changes of the past two decades have considerably altered the demands on medical and nursing services. Perhaps the most striking change has been the decrease in admissions to children's hospitals, fever hospitals, and sanatoria, and also in the number of home confinements. The following study shows how the pattern of home nursing has been modified in Birmingham since 1950.

The Changing Pattern

The number of new cases accepted by the service rose from 14,409 in 1950 to 20,192 in 1953 and then fell to 17,301 in 1957. The total case-load (the number of new cases accepted in one year plus the cases carried over from the previous year) rose from 16,084 in 1950 to 23,267 in 1955 and then fell to 21,139 in 1956 and 21,049 in 1957. The number of visits paid rose steadily, from 387,965 in 1950 to 674,317 in 1957.

These variations can be attributed to four main causes: (1) changes in the age-distribution of patients; (2) changes due to advances in medical treatment; (3) temporary changes in the incidence of acute respiratory illnesses; and (4) changes in the sources from which patients were referred.

Age-distribution of Patients

It has been fairly widely assumed that the increase in the number of old people has thrown a heavier burden on the district nurses. This is only in part borne out by our experience in Birmingham. Though among the new cases the proportion of patients over 65 rose from 35% in 1953 to 43% in 1957, the actual numbers of new cases in this age-group remained roughly constant—7103 in 1953 and 7363 in 1957. However, the total case-load of patients over 65 has risen by 16% since 1953 (8489 in 1953 to 9837 in 1957). As a result, the number of patients with diseases associated with later life has risen. The number of cases of heart-disease, for instance, rose from 1215 in 1950 to 2051 in 1957 and of cancer from 878 to 1006. Many of these elderly patients need the help of the home nurse for longer periods than the young patient with an acute illness; and in consequence, the number of patients carried over from year to year has more than doubled (1675 in 1950, 3748 in 1957).

A rise in the elderly and chronic sick increases the work of the service out of proportion to their numbers, for these patients need more nursing. Not only has the illness itself to be treated but during the care of these bedfast patients attention has to be paid to the prevention of deformities and pressure sores. Diet and hygiene must be supervised. More time must be given to ensure the patient is fully rehabilitated after the illness.

But it would be wrong to suppose that the greater part of the work of the service is the care of the elderly and chronic sick. In each year since 1953 more than 2000 children have been nursed, and in 1953 the number was 3422.

The number of preschool children fell sharply in 1953–54. Since then the figures have risen slightly but consistently from 1042 in 1954 to 1195 in 1957. Conversely, after a similar sharp fall between 1953 and 1954, the number of schoolchildren nursed fell slightly from 1119 in 1954 to 916 in 1957. No satisfactory explanation is evident.

Medical Advances

The introduction of antibiotics has enabled family doctors to treat more sick children outside hospital. But its most obvious result has been the rise and fall in the number of tuberculous patients nursed at home. This rose from 457 in 1950 to a peak of 1237 in 1953 and fell steadily to 443 in 1957. Between 1950 and 1953, because of the growing use of streptomycin, more patients were referred to the district nurses for injections. Also, active treatment could be started in early cases awaiting admission to a sanatorium. Since 1953 the number of cases of tuberculosis has fallen, and admission to a sanatorium can be arranged without delay. Consequently the demand of these patients on the home nursing service has waned.

The number of injections of penicillin given by district nurses has tended to fall, the figures for 1953 and subsequent years being 47,322, 43,878, 40,165, 32,415, and 33,495. This general decline, which has only been temporarily interrupted when the incidence of respiratory disease is high, seems to be due to the use of preparations of penicillin and other antibiotics which can be taken by mouth. Similarly, oral preparations are often now prescribed instead of injections of mersalyl and insulin. The treatment of tuberculosis with drugs taken by the patient unsupervised in his own home has not been wholly successful (Fox 1958, Wynne-Williams and Arris 1958). As Fox remarks, "to make a patient take medicine regularly for a year it is necessary to establish a new pattern of behaviour". This is precisely what the elderly and chronic sick may find difficult to do. In some of our patients with heart-disease self-administered oral diuretics have not successfully controlled their illness, and their doctors have reluctantly returned to injections of mersalyl. The few diabetic patients who have been changed from insulin to carbutamide have so far been more successful, possibly because strict self-discipline has become for them a habit of life. Because the attendance of the nurse ensures regular treatment and supervision, treatment by injection may, for many patients, continue to be preferred to self-administered drugs.

Prevalence of Acute Respiratory Illness

The level of respiratory illness in Birmingham has varied from year to year. Until 1953 the amount nursed by the service rose steadily. There was no special rise in 1951—the year with the highest number of deaths from bronchitis, pneumonia, and influenza. In 1953, the year when the number of deaths in the first quarter was the highest since 1950, the service nursed the greatest number of cases of respiratory disease. Since 1953 the number of patients nursed at home has fluctuated.

The nurses' case-load of respiratory illness is heaviest in the first quarter of the year. As one would expect, the number of cases appears to be influenced both by the severity of the weather and by epidemics of acute upper-

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respiratory illness. During the autumn epidemic of Asian influenza in 1957, the number of new cases attended was 49% higher in October than in August, visits 11·5% higher, and the number of penicillin injections 207% higher. In October, moreover, 252 days were lost by the nurses through respiratory illness (including influenza) compared with none in August. Working capacity was thus lowered just when the work increased.

Changes in Sources of Referral

From 1950 to 1953 the number of patients discharged from hospitals to the service remained roughly the same at some 2200–2600 per annum (11–16%). The rise in the number of new cases nursed was contributed almost entirely by the general practitioners—11,635 (81%) in 1950 and 17,549 (87%) in 1953. Since then the number of new cases referred by family doctors has fallen (16,205 in 1957), but owing to a sharp decline in the number of hospital patients referred direct to the home nursing service (739 in 1957) the proportion of patients referred by general practitioners has increased to 94%. These figures, however, do not reflect the true position, for since 1955 one of the city's hospital groups has referred its patients to the service (when they need home care) through the general practitioner. Nevertheless, the view of Godber (1958) that " since the trend of hospital practice is toward the encouragement of home care and early discharge from hospital, the home nurse is also more frequently required to continue treatment at home " is not sustained by our experience. Since 1950 there has been no consistent rise in the number of cases (either surgical or non-surgical) referred from the hospitals. This is rather surprising since early ambulation is increasingly practised in hospital.

The very large increase in practitioners' referrals between 1950 and 1953 is probably due to a number of causes. It naturally took people some time to learn that in the National Health Service the services of the district nurse were free. For the first time family doctors were able to explore the full possibilities of home care. The continued high level of their referrals since 1952 illustrates vividly that " home nursing is the most direct contribution made by the local health authority services to family practice " (Godber 1958).

Developments in the Service

The number of visits has increased almost in direct proportion to the increase in staff. If the part-time nurse is regarded as doing five-eighths of the work of a full-time nurse, and a student two-thirds, then the equivalent whole-time staff has risen by 203% (91 in 1950, 186 in 1957), and the visits by 174% (387,965 and 674,317). Each nurse now has a slightly lighter case-load than in 1950, and is better placed for using fully those nursing skills which make so much difference to the comfort and progress of the patient.

The following case illustrates the amount of care patients may now be given by the district nurse:

Mr. A, aged 51, was referred to the service on discharge from hospital after the insertion of radium needles for a recurrence of carcinoma of the larynx. Four years earlier he had undergone laryngectomy. At the beginning of our care he was visited twice daily. He needed general nursing, and in addition at each visit his tracheotomy tube was changed and cleaned and his operation wound dressed. Often the wound bled during treatment and the nurse had to apply pressure until this ceased. Later he became unable to swallow, and had to be fed through a nasal tube. Towards the end of his illness he had much pain and required analgesics by injection. In the last three weeks the nurse was visiting four times each day, spending five hours on his care.

Much time, too, may have to be given to rehabilitation:

Mrs. B, aged 65, developed a right-sided hemiplegia after a cerebral hæmorrhage. She was looked after by the district nurses under the direction of the general practitioner. At first she was visited twice daily for general nursing. As she improved a start was made with rehabilitation. Her relatives opposed this, feeling it kinder to allow her to stay bedfast, but after much effort the nurse won their cooperation. Walking exercises continued daily until she was well enough to go to hospital for physiotherapy. Now, some 18 months from the start of her illness, she can walk short distances with the help of tripod sticks.

With a lower average case-load for the nurses, there has been a rise in the amount of nursing equipment issued by the public-health department:

	1951	*1957*
Wheel chairs (various)	357	1126
Bedsteads	5	389
Mattresses	15	222
Lifting poles and chains	1	102
Walking-sticks (including tripod sticks)	Nil	141
Back rests	196	665
Leg cradles	44	245
Commodes	20	773

Not all of this was issued to patients nursed by the service, but it gives some indication of the equipment available to the district nurse. The loan service has never failed to supply her with an item for which she asked. As with the use of the home nursing service by the family doctors, so there has been an element of self-education in the use of specialised nursing equipment by district nurses, and the new emphasis on rehabilitation in the home has called for more apparatus. Patients who years ago might have remained bedfast are now using wheel chairs, tripod sticks, and commodes. Also mechanical aids have made it possible to nurse heavy immobile patients at home. The district nurse can help the disabled and the chronic sick to lead fuller and more independent lives.

Inadequacy of household equipment would often necessitate the removal of patients to hospital were it not for the loans of beds, bedding, and suitable clothes. The usefulness of lending equipment is seen in the following case:

Mr. and Mrs. C were a middle-aged couple. Mr. C was tuberculous and the district nurse visited daily to give him injections of streptomycin. Mrs. C was admitted to hospital with a cerebral hæmorrhage. On discharge she had a left hemiplegia and was incontinent. At the request of her family doctor the district nurse visited her twice daily and a home help undertook the main domestic duties. Only a double bed was available in the house, so a single bed with a lifting pole was obtained through the loan service. A back rest, a bed cradle, a mackintosh, and a bedpan were also lent. The domiciliary laundry service arranged a supply of clean bed-linen. As Mrs. C's condition improved the bedpan was exchanged for a night commode. She was lent a pair of special walking-sticks. She can walk about and do many things for herself and she no longer needs skilled nursing.

As this case-history shows, the district nurse does not work in isolation. The home help and the health visitor often assist in her task. The domiciliary laundry service is an invaluable aid. Often the patients' circumstances demand close teamwork:

Mrs. D, aged 73, was referred to the service in 1953 by her

doctor, for nursing care of an infected foot. She lived alone in an unfit house, near the centre of the city. The house was dirty and she herself was not clean. She was very independent, but within a few days the home nurse had persuaded her to accept the loan of toilet necessities and the help of the domiciliary laundry service. The health visitor responsible for the care of the aged was called in and arranged for a home help to come. Within days the old lady was not only on the way to full recovery but also clean and comfortable for the first time for many weeks.

These cases show that the district nurse can undertake quite complex nursing techniques in conditions of considerable social difficulty. She is not confined to " simple nursing ".

Conclusion

Many patients now admitted to hospital could be nursed at home, and many more patients could be discharged earlier to the care of the home nursing service. Much nursing which calls for a high degree of skill is already undertaken by district nurses, under the general practitioner and with the backing of the full local-health-authority domiciliary team; but home nursing can progress yet further if hospital, general practitioner, and the local authority can achieve full cooperation.

The high degree of knowledge and skill which is exercised by general practitioners and district nurses is not widely recognised outside these two branches of the National Health Service: for example, in the valuable work of McKeown and his colleagues on the care of the aged the possibilities of domiciliary care are assessed too low (Lowe et al. 1949, McKeown 1958). Research is needed to establish which patients may be best cared for at home and in what circumstances patients should be admitted to hospital.

Not only is home care less costly than hospital care, but (more important) any advance in domiciliary care increases the amount of sickness for which the family doctor assumes personal responsibility. Good home care increases the confidence of the patient in the doctor. To encourage the practitioner to deploy more fully his knowledge and skill will improve his status and will be of lasting value to the community.

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REFERENCES

Fox, W. (1958) *Tubercle, Lond.* **39,** 269.
Godber, G. E. (1958) *Lancet*, ii, 1.
Lowe, C. R., McKeown, T. (1949) *Brit. J. soc. Med.* **3,** 10.
McKeown, T. (1958) *Lancet*, i, 701.
Wynn-Williams, M., Arris, M. (1958) *Tubercle, Lond.* **39,** 138.

Influenza

The World Health Organisation reports that outbreaks of epidemic influenza during the past few weeks have not proved so severe, in any country, as those of the pandemic in 1957–58. Asian influenza occurred in Russia (where the peak of the epidemic was reached at the end of January), then in Poland, Czechoslovakia, Bulgaria, Greece, Israel, India, and Japan. In the United Kingdom, both A and B types of virus have been held responsible for the observed outbreaks, B being the commoner. Influenza B, reported in sporadic form in certain European countries during the last few months of 1958, occurred in epidemic form during January and February in Italy, Sweden, Denmark, the Netherlands, North Germany, Switzerland, Yugoslavia, and France. Everywhere the illness was mild or moderately severe and does not seem to have produced a striking rise in overall mortality.

Infectious Diseases in England and Wales

Disease	Week ended March			
	7	14	21	28*
Diphtheria	3	5	3	2
Dysentery	973	1027	1171	1005
Encephalitis:				
Infective	1	2	1	2
Post-infectious	8	—	6	5
Food-poisoning	112	126	131	109
Measles, excluding rubella	23,552	22,754	22,353	19,526
Meningococcal infection	37	28	30	21
Ophthalmia neonatorum	21	32	29	17
Paratyphoid fever	6	5	9	16
Pneumonia, primary or influenzal	2583	2039	1452	869
Poliomyelitis:				
Paralytic	9	11	8	14
Non-paralytic	—	1	3	4
Puerperal pyrexia	284	282	197	158
Scarlet fever	1208	1240	1084	996
Smallpox	—	1	1	—
Tuberculosis:				
Respiratory	444	638	647	646
Meninges and C.N.S.	6	4	9	4
Other	55	42	50	41
Typhoid fever	1	—	—	—
Whooping-cough	500	588	535	499

* Not including late returns.

Special Articles

THE REORGANISATION OF FRENCH MEDICINE

J. F. DELAFRESNAYE
M.D. Paris, M.B. Lond., M.R.C.P.

THE reform of French medicine—the Réforme Debré—was adopted by decree on Dec. 3, 1958, under the full powers granted by Parliament to the Government of General de Gaulle. This is the first major reform since the early 19th century and will involve not only the reorganisation of the medical curriculum, but also the creation of " university hospital centres " (centres hospitaliers et universitaires), the fusion of the hitherto separate university and hospital careers, the introduction of hospital practice and research on a full-time basis, and the expansion of research facilities and opportunities.

THE PRESENT SYSTEM OF MEDICAL EDUCATION

At present, medical studies last seven years. The French equivalent of the premedical year is done at the faculty of science. From the moment he enters the faculty of medicine, a medical student leads a double life: in the morning he attends clinical courses at hospital and in the afternoon lectures and practical courses at the university.

The university course is mainly theoretical. The first two years are devoted to the fundamental sciences, the third to pathology, the fourth, fifth, and sixth years to clinical medicine, surgery, the specialties, psychiatary, public health, and therapeutics. Each year, a student must take examinations on the subjects taught during the year. At the end of his studies he must take his " clinicals " and write a thesis for his M.D.

At hospital, he attends lectures in pathology, clinical medicine, and surgery, but there is no coordination between the university and hospital lectures. Ward rounds, clinical demonstrations, and attendance at operations complete his hospital training. In fact, an ordinary student will have few opportunities to come close to patients and to be given responsibility for their care except during the last year of study when he is appointed " student intern " in one of the smaller hospitals.

This is why a student worth his salt will take the competitive examinations held by the Hospital Boards—the Assistance Publique in Paris and similar bodies in the provincial university towns.

The first two of these examinations—the *externat* and the *internat*—are taken before qualifying. An externe is entrusted

with the care of patients and holds a post of responsibility and receives a small salary for his services. An interne holds a position equivalent to that of house-physician or house-surgeon but has rather more responsibilities, and he also receives a salary.

The standards of these examinations are high, and externes and internes form the backbone of French medicine. Roughly 1 student in 5 becomes an externe and 1 in 20 an interne. After working for three or four years, an interne, although technically an undergraduate, has reached a standard equivalent to that of M.R.C.P. or F.R.C.S. The internat is essential for a hospital career.

This duality in medical studies which is evident during the undergraduate years continues after qualification.

The university recruits its teaching staff by competitive examinations and the hospitals their physicians and surgeons by further competitive examinations. Those who want both an academic and a hospital career must take the two sets of examinations.

It is not an unfair generalisation to say that teachers in the fundamental sciences are secluded in their university departments, and hospital physicians and surgeons torn between their hospital commitments and their private practice.

Over the years, the number of teachers has not risen as rapidly as that of students, and the situation is worse in Paris than in the provinces: Paris claims 45% of medical students but only 25% of teachers.

These are the raw facts which had to be faced by the committee headed by Prof. Robert Debré.

LA RÉFORME DEBRÉ

The two fundamental pillars of the reform are (*a*) to revise the curriculum and to build "university hospital centres" and (*b*) to fuse the hospital and university appointments which will be held full-time.

The New Curriculum

No final decision has been taken yet but medical studies will very likely be divided into three "cycles".

The first cycle will last two or three years and will be devoted exclusively to the basic sciences and to clinical signs. There will be no hospital work at first, and teaching will be given in the existing buildings of the faculties.

The second cycle will last three years and will be held in the new university hospital centres. All students will have to perform the duties of today's externes, but the title of externe will be reserved for those students who get the highest marks at their university examinations. All students will have to spend one year as a "student intern" at the end of their studies.

The third cycle would be aimed at training research-workers and, it is hoped, will be arranged in collaboration with the faculty of science. It would lead to a doctorate in biological sciences.

The internat will remain as it is today and will continue to be the portal of entry for clinical careers.

University Hospital Centres

A certain number of hospitals will be transformed into university hospital centres. This will require the building of lecture halls, laboratories, libraries, common-rooms for students and for teachers, restaurants, and so on. They will become in effect medical schools, except in respect of the basic sciences.

It is realised, of course, that the university hospital centre is a compromise but this cannot be avoided if the best use is to be made of existing buildings and facilities. When new universities are created, the university hospital centre will cover the entire field of medicine.

Fusion of Hospital and University Careers

There are today many more highly trained hospital physicians, surgeons, and specialists (who have no teaching duties) than university lecturers and professors in the clinical disciplines. Consequently it was decided to fuse the academic and hospital careers. Physicians and surgeons will all have teaching duties to perform and the fundamental scientists will be given routine duties in the new university hospital centres. In addition to increasing the number of clinical teachers this decision will open up the hospitals to the fundamental sciences.

The teaching staff, whether clinical or basic, will be recruited on a national basis, thus enabling exchanges to be made between the universities. All will work on a full-time basis. This is the innovation which created the greatest controversy but it is now settled. The change-over will be gradual and everyone will be given an opportunity to retain his present status or accept a full-time appointment under the new system.

Every member of the university and hospital staffs will receive a salary from two sources—part from the ministry of education and part from the hospital boards. In the clinical branches, doctors will be permitted a few private beds in their departments and will be allowed to do urgent domiciliary visits. Pathologists will be able to charge for their examinations on private patients whether inpatients or not.

Finances

The financial implications of the reform are great but the Government is determined to meet them. Considerable sums will be required to build the new university hospital centres. In Paris, where the situation is critical, at least three centres will be built within the next three years. Money will be required to pay the salaries of the clinicians for their new teaching dutes. Finally, research must be supported on an increasing scale and new senior and junior appointments created, principally in the fundamental sciences.

The Prospects

At first the reform met with considerable resistance, which has now subsided; and everybody is cooperating to make it a success. The broad lines of the reform are clear but many details remain to be filled in. The French system does not allow various experimental methods to be introduced in different universities, so the responsibility placed on the planning groups is great. Within ten years, the reform which will change the face of French academic medicine must be an established fact.

HEALTH IN SCOTLAND

ALTHOUGH the general trend in Scotland's health [1] continues to be favourable, lung cancer and coronary atherosclerosis are causing concern, and "the incidence and death-rate of chronic bronchitis are high—almost the highest anywhere." Men over 45 are the only section of the population with a rising death-rate, and this is almost wholly due to lung cancer and heart-disease.

On smoking the report says:

"... if all cigarette smoking were to stop tomorrow, the result in diminished incidence of lung cancer would not be immediately apparent. A careful study of the evidence, however, leads to the conclusion that if cigarette smoking, and other smoking as well, were to decline, ultimately the result of this would be reflected by a reduction in the death-rates for lung cancer. Especially would this be so with regard to the younger generation ... and they would be well advised not to begin smoking at all. It is disquieting to read about smoking habits developing in school children ... There is no

1. Report of the Department of Health for Scotland for 1958. H.M. Stationery Office, 1959. Pp. 111. 5s. 6d.

doubt that the smoking of cigarettes increases the liability to chronic bronchitis. . . . "

The infant-mortality rate at 27·7 per thousand births is the lowest on record for Scotland. In Glasgow it was 35, and in planning, the biggest single factor in Scotland is the need for dispersing population and industry from Glasgow.

Of the 20,779 patients in Scottish mental hospitals at the end of 1957, three out of four were detained compulsorily in the first instance; 17,370 had been in hospital longer than a year; 13,551 longer than five years; and 7376 longer than fifteen years. " With increasing knowledge and understanding, improvements are being achieved in the condition of long-stay patients, and there is an increasing reluctance to write off a chronic patient as hopeless or incapable of improvement. By active treatment and rehabilitative measures some surprising results have been obtained."

Personal Papers

ON BEING SECONDED

I LIKE Africans, instinctively, intuitively, and perhaps irrationally. Therefore, when I happened to see the advertisement asking for a pinealoscopist " to help organise a comprehensive pinealological health service " in Melanoville, I showed it to my wife. I had been a consultant for almost ten years, and, if I was going to learn and do something quite new, I had better do it now. It seemed a great opportunity, and a challenge, and a job worth doing. There were other reasons—some banal, some pompous, and some no doubt hidden in my subconscious. We needed a change, and were fed up with living in suburbia. This was a perfect chance to leave that desirable detached residence of ours, and to move back to town when we came back. And in some obscure way I felt that " we " now had a duty to help the emergent countries on their way to independence, medical and otherwise. There seemed no reason why they should not be taught by " us ", rather than by Americans, Germans, or maybe you-know-who.

The pay looked good on paper; but, even allowing for the lower income-tax, I would only get exactly what I got here; and at that stage, many months ago, I did not foresee the financial chaos I was heading for. You get no outfit allowance if your pay is more than £1524, and you, and your wife, certainly will need a new outfit—in the end it came to over £300.

So I applied for the post, giving three medical referees, two personal referees, and a list of posts held since 1946, as requested. A whole handful of very standard forms must have been sent out by the Colonial Office, not only to my referees but also to the (lay) secretaries of several hospitals I had worked in years ago. I suppose everybody must have attested to my honesty, sobriety, and lack of major moral flaws, because in due course I was asked to attend the appointments committee. I don't suppose anybody else applied—an opinion held and voiced by several kind colleagues. Anyhow, I was " provisionally selected " for appointment. The next thing was a delightful medical examination. The very eminent senior physician did listen to my heart (" what a dull fellow you are "), and I suppose he did something with the urine I passed for him; but most of the time he reminisced about Singapore in—was it 1902? Things certainly seemed to have changed.

* * *

So far, so good, but from that moment the gilt began to wear off the gingerbread. I went to my S.A.M.O. and explained why I wanted to be seconded for three years. Yes, he thought his Board might agree to a secondment. Other Boards were not that enlightened, but his was. He hoped I had considered that, for all he knew, great reorganisation might take place in the pinealological world while I was away. Also, for all he knew, my going might lower me in the estimation of my senior colleagues. Obviously, he said, I would be out of the limelight at the R.S.M., and certainly out of the running for a merit award during those three years. The thing to do would be to talk to Professor O'Catheter, doyen of British pinealoscopy, and to Dr. McTubing, chairman of the board's Pineal Advisory Committee, so as to " get their reaction ". Furthermore I would have to persuade my management committees to let me go; and lastly it was, of course, up to me to produce the locum who would do my work during those three years. He himself had no idea where such a locum could be found. And would I please remember that if I did find a locum, he would have to be acceptable to Prof. O'Catheter, to Dr. McTubing, to the Regional Board, to the Management Committees, and to my colleagues at my various hospitals.

I had read about the Senior Registrar problem and had felt sorry for those unfortunates who were eking out a precarious living waiting to get their foot on the bottom rung. Now I know better. There is no such problem. Week after week, in mounting excitement and exasperation, and with a rapidly increasing consumption of gin and ' Seconal ', I contacted one unfortunate after another, either directly or through their chiefs. I remember the names of fourteen, but there must have been more. Mind you, there was the compensation of speaking to more big white chiefs than ever before in all my life.

It would be tedious to enumerate all the reasons why either the registrars, or their chiefs, were (regretfully) unable to oblige. Two highlights must suffice. One very eminent chief declared that his registrar was willing (he was—I rang him up), keen, and suitable, but that he feared the necessary journey to my hospital would prove too much of a strain for the young man. The other, equally eminent, strongly recommended his senior registrar for the locum post, yet apparently gave this registrar an impression that it would be unwise to accept—it might jeopardise his future career. I now began to have some idea of what it must be like to work in a teaching hospital. I knew about the chief's absolute power, and the assistants' serfdom, in German universities, but had naïvely imagined that this only happened abroad.

Not that I did not see the registrars' difficulties: the Board insisted on a gentleman's agreement to do the job for at least a year, and for the whole three years if possible. During that time other jobs might turn up. On the other hand, nobody—not even the Board—could really tie them up: the contract would allow three months' notice either way. So far as I could see they seemed to have little to lose—unless, of course, working at the Prince Peripher constituted a kind of guilt-by-association which might debar them from loftier jobs later on. At that stage I was also blissfully ignorant of the extraordinary mental game of chess that goes on in the minds of registrars working in the anoxic heights of teaching hospitals: " old Addiscombe will retire from St. Mountview in March, and Dr. Hunter will apply, but probably won't get it, but probably he'll get the Royal Amherst job. Dr. Frobisher will then try to get Hunter's old job at the Gerard General,

and then, of course, I might stand a chance of his job at Laburnum and Langham ". Thank God I got in before the appointed day.

* * *

Finally, two probable runners emerged, both senior registrars. On the subject of their pay, the Board wrote: " There is no way by which a clinician not holding a grading of consultant can be paid consultant rates for locum work ". If these two were not prepared to do a consultant's work, and take a consultant's responsibilities, on S.H.M.O. pay, the Board were " afraid that unless there is some way of providing alternative locum cover it would appear that we cannot proceed further with the question of your secondment to the Colonial Office ". Six months had now passed since I saw the advertisement; the strain was beginning to tell, and there had been a further increase in my consumption of alcoholic and other sedatives.

However, all turned out well; one senior registrar got his foot on the ladder just in time, and as his first rung amounted to only two sessions he could do most of my work. The other senior registrar, feeling and hoping (I trust with justification) that doing consultants' work, though not getting paid for it, might prove useful in the future, resigned himself to the S.H.M.O. pay scale.

The next hurdles were the various hospital committees. Dr. Shadrach would under no circumstances have anybody from Gert's, Dr. Meshach would find young Dr. Thor unacceptable, and Dr. Abednego hoped that I would not suggest Dr. Odin. And, quite definitely, the Medical council of the Prince Peripher would not accept a senior registrar: it was either a consultant or nothing. (" In any case," they said, " if a senior registrar does your work for you, the Board may well turn round when you come back and say that clearly a consultant is not necessary."—Who knows, maybe they have got something there?) Furthermore, the committee would insist on the incumbent committing himself to the whole three years. It needed a lot of talk to make it clear that established consultants who had nine sessions to spare did not grow on trees.

* * *

From the beginning, my relations with the Colonial Office had been deliciously vague. At the appointments committee the lay member had told me that the job was mine, that I could plan it in any way I chose. All I knew about it was that there would be some 300 outpatients a day, that I would have to cooperate with the (very able) African M.O.H., the Melanoville Town Council, the Department of Astronomy, the Department of Pineal Welfare, and various " voluntary agencies ". I would be consultant pinealoscopist to several hospitals, and take charge of a new one—when built. And that was that.

I did, however, receive two booklets. One on the duties of Governors and Officers, which lays down in detail that bribes cannot be accepted, no matter how they are wrapped up. The other little book (bearing the legend " A poisonous insecticide has been used in binding this book ") is entitled *Hints on the Preservation of Health in Tropical Countries*. The publication date is 1957. It contains, inter alia, a magnificent photograph of " *Glossina palpalis*. Rob.-Desv. ×4 ", a photograph of a mosquito net (by kind permission of Messrs. Way & Co.), and a list of the " most essential medicines and other articles required ". The list starts: 1 lb. Epsom salts, 100 Cascara tablets, 100 Aspirin tablets, ½ lb. Castor oil, ½ oz. Chlorodyne (O *National Formulary*!). The sun should never set on a people who put first things first.

But more exciting than all this were those delightful letters which began " Sir, I am directed by Mr. Secretary L.. B.. " and ended " I am, Sir, Your obedient servant, signed, Amanda ffoulkes (Miss) ". How *does* one answer them?

* * *

Finally, the reaction of one's friends and colleagues. Without one single exception they ask, after about five minutes' general chat, and often indirectly, and very tactfully, if my wife is coming with me. The tradition of the black sheep running away to sea is still very much with us. The majority take a very keen interest, say that they wish they were 20 years younger (they are usually my age), and say that they would go themselves if they had no kids to educate. Even so, I had the feeling that an idealistic motive is distinctly non-U in 1958.

The most pleasant surprise was meeting those who " had been there ". A closely knit, cheerful, friendly, and hospitable fraternity, full of enthusiasm and energy. I only hope I can live up to their standards.

Symposium

HEREDITARY METABOLIC DISEASES

A SYMPOSIUM on Biochemical Aspects of Hereditary Metabolic Diseases was held by the Association of Clinical Biochemists, jointly with the Biochemical Society, in Oxford on March 21. Mr. J. R. P. O'BRIEN and Prof. E. J. KING were in the chair.

Genetics and Metabolic Variation

Dr. H. HARRIS (London) derived the one-gene one-enzyme hypothesis from Garrod's original concept of inborn errors of metabolism and illustrated it with the recently studied defect of cystathioninuria. In this disease there appears to be a block along the pathway by which methionine is normally converted to cysteine. The intermediate, cystathionine, cannot be broken down, accumulates intracellularly, and is excreted in large amounts in the urine.

Mutation is usually thought of as altering the character of a normal gene in such a way that the synthesis of the enzyme it controls is prevented. It now seems probable, however, that the mutant gene may on occasion lead to the formation of an unusual enzyme. An example is the atypical pseudocholinesterase recently found in succinylcholine-sensitive individuals. This differs from normal pseudocholinesterase both in its substrate specificity and its inhibition characteristics. Succinylcholine-sensitive individuals are homozygous for the gene producing this abnormality. The heterozygotes, who amount to 3–4% of the general population, have both the usual and the atypical enzymes in their plasma.

Phenylketonuria

Dr. L. I. WOOLF (Oxford) reviewed phenylketonuria, a congenital absence of phenylalanine hydroxylase. Instead of being changed to tyrosine, phenylalanine accumulates in the body-fluids and some of it undergoes subsequent changes into phenylpyruvic, phenyllactic, phenylacetic, and *o*- and *p*-hydroxyphenylpyruvic acids. The well-known clinical manifestations may be arrested by prompt reduction of the dietary phenylalanine intake to minimum requirements. Treatment is aimed at keeping the blood-phenylalanine level within normal levels, and is controlled by periodic blood estimations.

Maple-syrup-urine Disease

Dr. WOOLF suggested that this disease may be due to a block in the oxidative decarboxylation stage of the metabolism

of valine, leucine, and isoleucine. These aminoacids, with their corresponding α-keto- and α-hydroxy-acids are excreted in the urine. The incidence of this abnormality may be higher than that reported, since in most cases the patient dies early and the disorder may remain undiagnosed.

Wilson's Disease and Hæmochromatosis

Dr. A. G. BEARN (New York) described the findings of Debré and coworkers in 30 patients with hæmochromatosis and 67 offspring of patients. No sex differences in serum-iron levels or iron saturations were found up to the age of 15; after that age the mean level for sons was higher than for daughters, and, while half the sons had a normal iron metabolism, half showed abnormalities intermediate between normal controls and patients with hæmochromatosis. The disease is likely to be inherited as a dominant with pronounced sex limitation; when found, rarely, in young women it is probably in homozygous form.

The lowered copper-binding found in Wilson's disease is due to an inability to synthesise ceruloplasmin. This leads to deposition of copper in the liver, brain, and kidneys; sometimes Fanconi's syndrome is simulated. Transmission is probably in an autosomal recessive fashion, but carriers of the abnormal gene may have slightly impaired capacity to synthesise ceruloplasmin. Ceruloplasmin levels can be increased by administering œstrogens—an interesting example of the way in which experimental modification of the environment may alter the expression of the abnormal gene.

Hartnup Disease

Dr. I. SMITH (London) said that in Hartnup disease the characteristic aminoaciduria is of renal origin and precedes clinical symptoms. Biochemical comparison with cases of true pellagra shows that earlier views on the similarity of the two conditions were mistaken. All English "pellagrins" investigated up to now have proved to have Hartnup disease. The primary disorder in the disease may be the absence, controlled by a rare recessive gene, of an enzyme in the normal pathway of tryptophan metabolism; the abnormal appearance of indolylacetic acid may be due to an attempt to metabolise tryptophan by an alternative pathway. The clinical picture may be explained by a deficiency of normal metabolites plus poisoning of the renal tubules by abnormal ones.

Cystinuria

Dr. G. A. ROSE (London) defined cystinuria as a single condition in which urinary excretion of cystine and lysine (and frequently also of arginine and ornithine) is increased, but in which all the other urinary aminoacids are excreted in normal amounts. The disease is transmitted by one or more rare recessive genes, and all homozygotes excrete an excess of the four aminoacids. In some families heterozygotes excrete excess cystine and lysine only; the condition is then called incompletely recessive. In other families the gene behaves as a true recessive, and heterozygous carriers have normal urinary aminoacid patterns. Cystinuria may be due to a deficiency in an enzyme system which acts in the renal tubular reabsorption of these diaminoacids; the incompletely recessive heterozygous cystinuric has a smaller amount of functioning enzymes, and in these conditions arginine and ornithine are reabsorbed preferentially to cystine and lysine. All the clinical effects are due to cystine being deposited in the urinary tract.

Albinism

Prof. T. B. FITZPATRICK (U.S.A.) said that it is now fairly certain that the structural basis for melanogenesis is present in generalised albinism, so the structural-defect theory does not offer a satisfactory explanation. Albinism is explicable as a metabolic defect the biochemical lesion of which consists in failure of melanocytes to synthesise tyrosinase, the copper-containing oxidase required for the conversion of tyrosine to melanin. On present evidence this is due to the absence of the gene (in the melanocyte) which is required for the synthesis of tyrosinase on the melanin granule.

In England Now

A Running Commentary by Peripatetic Correspondents

Z STANDS for Zurich, where last month the European Productivity Agency of the Organisation for European Economic Cooperation held a conference to introduce to both sides of industry the idea of fitting the work to the man. The flight put our mind on the right lines straight away. "Mind your head", said the officer at the top of the gangway as our modest 5 ft. 8 in. approached the door. During the journey we looked in through the window on to the flight deck; and there, nestling on the throttle levers, was a cup of coffee—a nice blend of pharmacology and ergonomics. We were told later that this human habit had, indeed, caused a modification of the design, in that the levers were now fitted with waterproof gaiters to avoid spilt coffee interfering with the mechanism.

As was only appropriate the planning and organisation of the conference were excellent, and the firm and pleasant chairman ensured that the proceedings ran smoothly. He sat, usually alone, in the front row and heard each paper delivered, occasionally twirling his hands to speed up a slow speaker, or dashing out to find a tardy projectionist. A little to our surprise, the idea that work can be designed to fit the human being was received favourably by both management and workers. We left feeling that, however difficult a common market in merchandise may be proving, a common market in ideas round the biology of work was, indeed, more than possible.

Apart from more solid scientific gains, we carried away some pleasant, if less weighty, souvenirs. It was a delight, for instance, to find that the programme pleasingly described a speaker as being from "Maison Brown Boveri & Co.", Baden, and to realise with a shock that the prefix "Maison", which we thought applied only to ladies' hats, applied also to turbo-generators. Weaving in and out among the delegates were soft-spoken men with English names in foreign clothes, from W.H.O., on the lookout for good lecturers. Grave international complications were observed as two delegates became inextricably entwined with their headphone wires, tethered to the bench at short range. But the climax of the meeting came when a member of the British delegation rushed down the steps of the auditorium bearing what looked like, from a side view, some celery wrapped in tissue paper, to present it to the not exactly blushing Swiss organiser. This was a model of time-and-motion study—with a minimum of time and a maximum of motion. One or two of us suggested that he should have kissed her, but a senior French colleague wisely remarked that, although in France this would have been entirely proper, in Switzerland (for all he knew) it might well have been a crime. Was it true, the lady asked us, on saying goodbye, that we were one of the fathers of ergonomics?

* * *

Brooding over the proposed standard form for book reviews which a fellow peripatetic kindly offered a fortnight ago I suddenly realised that an important law governs this specialty—the length of the review varies inversely with the size of the book, judged by the number of pages.

According to this version of the law, a standard reference work liberally illustrated and bound firmly in cloth (London: Stinkfolder & Pebbledash, Pp. 1648; Lb. 6¾, 183*s*.) would be reviewed as follows:

> "The popularity of this work is reflected by the call for yet another edition, the third in 10 years. It amply lives up to the standards of its predecessors."

Sandwiched between the two sentences may be a list of the chapters that have been rewritten. If the reviewer happens to hate the author's guts, a long rebuttal of some statement on p. 1345 may be included. This same type of review is also appropriate for those verbatim reports of learned conferences which are often about as interesting to read as the debate on the Supplementary Estimates in *Hansard*. Medium-range textbooks call for a slightly longer review, because there are more of them and a kindly journal will try to guide its readers. But a short course of lectures, which some chap has had

printed on spec, calls for a good half page, because most of the things he says are doubtful and he has not the space to discuss his evidence. Slim pamphlets on things like Colour, Penal Reform, Sex, and so on, call for some columns of cogent editorial discussion and weeks of dispute in the correspondence columns.

Statistically minded readers may care to work out exact formulæ for my law, bearing in mind such variables as (*a*) status of reviewer (I guess the older and more famous, the shorter); (*b*) coefficient of friction between him and author expressed in therms: (*c*) height in centimetres of pile of other reviews pending on editor's and reviewer's desks; (*d*) price of book—this is not necessarily related to length (with some books we wonder if *anyone* will *ever* buy a copy, apart perhaps from the librarian of the R.S.M.); (*e*) known paranoid traits in any of the 4 contracting parties.

* * *

Overhead in the local.—" I've been proper poorly these last few weeks. First of all I got the 'flu and after that I went down with influenza . . ."

* * *

He pulled off his shirt in the consulting-room and there was the scar I had not set eyes on for eighteen years. Right along the line of his seventh rib on the left it was. Much whiter now, and much less embarrassing for everybody. His face had seemed vaguely familiar as he walked in for his insurance examination, but I plead the excuse that it was upside down and a lot less pink when I last saw it emerge from my anæsthetic mask, trolley-bound back to Side-ward K. So that was who he was, the only British officer I ever knew to be bayoneted by his own side.

He was a stocky virile little chap of the scrum-half type. What he lacked in inches he made up in guts and self-confidence. If the parade ground was not enhanced by his appearance, he had his own peculiar contribution to make to Britain's war effort. He specialised in unarmed combat. Those seasons in the mud on the blind side of a famous pack of forwards had not been spent in vain. Brawn had writhed before brains in many a friendly match, and what he could do to the enemy was a much valued factor in our war potential. So much so that he was selected to lead a circus of unarmed combatants around the more conventionally minded units to give demonstrations of his art. The most popular turn was to pick out the beefiest-looking private soldier from the spectators, and invite him to do his worst with a fixed bayonet. That always went down well with the troops. A quick side-step by the expert, an even quicker tug on the weapon, and another astonished gladiator went base over apex to bite the dust. So it went on with great gusto up and down the Commands until some brass-hat had the bright idea of showing the Army's prowess to the Home Guard. Off went the circus to deepest Somerset one Sunday afternoon. The theory of unarmed combat was expounded to the local defenders, and then the stooge was picked for the fun. He took up his rifle, fumbled the bayonet into place, and stood ready with a most unsoldierly guard. A whistle blew. The first attack was honours even: neither party made contact with the other. The second was just too easy. A lazy curving swing with a terminal flick nicely hooked the instructor from any further part in the proceedings. " 'Twas simple," remarked the Home Guardsman, " Oi bain't using a pitch fork all me life for nothin'—'twas just he doan't know proper way to keep hisself clear at haytime."

* * *

Ban the nurses' yakity-yak,
Ban high-heels that clickety-clack,
Oil the doors and tighten screws,
Grease all wheels and whisper news.
Rubber dustbins, a coir mat,
Plastic bowls and this and that
Will help to rid us of the din
And let us hear a dropping pin.
But please remember, this I crave,
Noise means life—silence the grave.

Letters to the Editor

FAILURE OF STERILITY IN HOSPITAL WARD PRACTICE

SIR,—Much of what Professor Hare says in his letter of April 4 is right, but there is a danger that it may mislead others. He is right in saying that better sterilisers will not necessarily mean less hospital infection, that many infecting microorganisms can sometimes be killed by very short exposure to heat, and that sometimes faults in sterilisation can be put right with a little common sense and at a low cost.

But none of these points has any bearing on the arguments for or against central sterile supply departments. These must stand or fall on their own merits. Many so-called sterilisers in our hospitals today simply do not sterilise; many so-called sterile goods are not sterile by any accepted standard. No improvements can be expected until sterilisation is treated much more seriously than it has been in the past. In most hospitals " sterilisation " is carried out in many different departments by methods and by individuals differing greatly in efficiency and reliability. This does not make for the regular provision of invariably sterile goods. Some articles can be more easily sterilised than others; but for the reliable sterilisation of dressings, gloves, many kinds of instruments, and other things, rather complicated and bulky apparatus is necessary. This apparatus must be centrally placed and controlled by skilled and conscientious operators capable of organising the regular supply of sterile goods throughout the hospital. This ideal may be unobtainable in old hospital buildings but in a new hospital anything else is false economy.

Boiling-water " sterilisers " cannot be relied upon to sterilise and are positively dangerous if not properly used. They should be used only where more efficient methods are not available or in emergency.

Guy's Hospital Medical School,
London, S.E.1. ROBERT KNOX.

SIR,—The demonstration by Professor Hare and his colleagues of unsuspected reservoirs of staphylococci which may be dispersed into the surrounding air is of great epidemiological importance. Professor Hare is almost certainly right when he states that most of the infections acquired in hospital " are due to organisms on the fingers or clothing of nurses and doctors that have come from themselves or someone else and not to organisms surviving on inadequately sterilised instruments or dressings ". If this is accepted it means that cross-infection cannot be prevented by any one single method and that all hospital staff will have to impose on themselves a stricter discipline. With such cooperation of the staff many of the practices required can be put into operation immediately but others will need to wait for the expenditure of considerable sums of money.

Professor Hare is to be congratulated on the results achieved through cooperation and at such little expenditure of time, effort, and money. Many hospitals are working along similar lines, but to my mind this should not deter them from a searching reassessment of their sterilising procedures and, if the need is substantiated, from establishing central sterile supply departments. Our preoccupation with staphylococci must not allow us to ignore the recognised though fortunately smaller risk of infection by spore-bearing organisms which are more difficult to destroy. The Nuffield team and Dr. Darmady

and his colleagues have shown the need for ensuring that sterilising equipment can be and is operated efficiently. If the so-called sterilisers cannot be guaranteed to sterilise, many of the hospital staff will question the use of their submitting to the necessary discipline.

Central Middlesex Hospital, London, N.W.10. J. D. ALLAN GRAY.

INFECTION IN HOSPITALS

SIR,—The serious problem of infection in hospitals has received much attention, and the recent Central Health Services Council report on staphylococcal infections contains much wisdom; but how many of its recommendations are likely to be fully implemented?

As an old-fashioned doctor I sometimes wonder if the modern aseptic methods are not based on a counsel of perfection and are not really practicable, except perhaps in teaching hospitals with an adequate highly trained staff. In some of our hospitals less fortunately placed, would it not be worth trying to revert to some of Lister's old antiseptic methods? Perhaps a larger expenditure on carbolic acid might help some of our problems.

Reigate. T. W. PRESTON.

HAZARDS OF WATER ENEMAS

SIR,—Your leader of March 14 was timely. The danger of water intoxication is still too little realised in the treatment of the various forms of megacolon. But some of us have felt for several years that such enemas are not only dangerous in these conditions but relatively ineffective.

Rectal washouts are used instead. A few ounces of saline are run in from a funnel by gravity, and this fluid *must* be syphoned back before the next amount is run in. In this way 6–20 pints may be used daily without risk of intoxication, depending on the age of the child and his tolerance. This is much more effective in emptying the bowel.

It appears that some authorities teach that the procedure is called an enema if fluid is injected by syringe and a washout if run in by gravity. In each case the child is left to return the fluid by his own efforts. These efforts will often be inadequate in colonic inertia or true Hirschsprung's disease. The essential of the technique which has been used at Great Ormond Street and Queen Mary's, Carshalton, is that the fluid is syphoned back and a large amount is not left in the bowel at any one time. The danger of rapid massive absorption is thus averted.

But not all enema reactions seem to be due to water intoxication. A number of children have had a sudden collapse during or shortly after a washout when this cause has seemed impossible. For example, one child had had only 6 ounces of saline instilled. On two occasions serum-sodium was measured during the crisis and was normal. These children have been seized with a severe abdominal pain followed by collapse sometimes with unconsciousness or fits, a rapid weak pulse, and pale skin. Pupils have been contracted or dilated. Respiration has been shallow and a few had acute pulmonary œdema needing urgent treatment. The collapse has been followed by the passage of astonishing copious volumes of fluid fæces. It has sometimes seemed that plasma infusion has saved life at this stage. The cases have been of aganglionic Hirschsprung's disease and various types of colonic inertia. The common factor seems to have been the presence of an impacted fæcal mass at the time of stimulation by the washout. I have wondered if this is some reflex nervous effect with an "obstructed labour" on the mass and a reaction in the colon akin to the acute dilatation of the stomach. I feel that large fæcal masses should always be removed by evacuation under anæsthesia before washouts begin.

The suddenness of the attacks has led to their inadequate investigation as yet. But I feel that the comments of your readers in this serious emergency may be invaluable. It is my belief that the impression that all "enema collapses" can be explained by water intoxication might lead to a false sense of security.

London, W.1. H. H. NIXON.

SIR,—Your leader and Dr. Simister's letter of March 28 prompt me to report a potentially dangerous practice.

A young woman attending the private patients' department of a London teaching hospital for treatment of a recurrent genital cancer developed intestinal pain and bleeding for the diagnosis of which a barium enema was ordered.

She was given the address of a so-called medical institute and asked to arrange to have the bowel washed out there before presenting herself at the hospital X-ray department.

She said that at this address she was placed sitting on a specially designed w.c. and water was injected upward. She said she was told that a 20- or 30-pint washout was customary. However she suffered such intense pain that the lavage was discontinued. No medical advice was obtained. The subsequent barium enema was agonising, but the radiologist expressed little interest in this pain. Fortunately for him or her the gut did not perforate.

A few months later the patient died of her cancer. She insisted that the pain inflicted by these two "enemas" was more acute than any caused by the disease.

Perhaps the radiologists will now take the responsibility of prescribing exactly how the bowel is to be cleansed, with due regard to the size and condition of the patient. They may consider using the 4-oz. phosphate enema employed by Dr. Simister.

Public Health Laboratory, Edmonton, London, N.9. MAIR THOMAS.

THE FUTURE OF CHILD GUIDANCE

SIR,—I wish to concur with the points raised by Dr. Neville-Smith in his letter of April 4. For many years it has been the practice to allow direct referrals by parents to the Darlington and Sunderland clinics in which I work. The number of such referrals has always been manageable and indeed is usually less than the 11% mentioned by Dr. Neville-Smith.

I would make a plea for the widest possible area of referral. In the clinics in which I work probation officers, children's officers, pædiatricians, and others all enjoy direct access to the clinic, with benefit to both sides. In every case the family doctor is kept in the picture and his referrals are encouraged.

Durham. L. W. ROBINSON.

SIR,—I think you are incorrect in assuming, in your leading article of March 21, that there is universal condemnation amongst child psychiatrists of those recommendations of the Ministry of Education circular which you quote. A large number of child-guidance clinics in this country function very happily on a "joint user" basis between regional hospital board and local education authority; many of these clinics do excellent work in addition.

The difficulty appears to arise from your attempt to equate child psychiatry and child guidance. The former may rightly be regarded as a specialty of medicine. But child guidance (of which child psychiatry is an essential and integral part) is a widely based multidisciplinary approach to the problems of the child in relation to his total environment.

If this concept is accepted, the remaining recommendations of the circular fall into their proper perspective. Of

course, the family doctor and the pædiatrician should be in the forefront of preventive mental-health work with the child; but equally important figures in this task are the teacher, the school medical officer, the probation officer, the health visitor, the children's visiting officer, and many others, with the parents neither the last nor the least of these. Any one of these may well recognise, and need guidance on, the earliest stages of disturbance in the child. If it is to function adequately a child-guidance service needs to act in a consultative role to any or all of these workers. In the view of many child psychiatrists, this is as important a function of the child-guidance clinic as is its therapeutic one. And the clinic team cannot adequately fulfil this preventive function without close, personal, direct contact with all those concerned with the child.

Nottingham. T. A. RATCLIFFE.

MENTAL HEALTH BILL

SIR,—None of your correspondents has yet said that any of the younger medical superintendents have behaved in a discourteous way towards their consultant colleagues. I am sure that colleagues in a hospital cannot always be in complete agreement but if they cannot come to some acceptable compromise between themselves perhaps the fault does not lie entirely with one of them.

It is all very well to say that medical superintendents are bad and should be abolished, but the disadvantage of this is that, as with the bath water and the baby, if the medical superintendent goes, so does medical administration. None of the suggestions made will compensate for the loss of a medical man as the chief officer of the mental hospital. The chairman of a medical advisory committee and a medical superintendent appointed for a limited period would lack the authority in the eyes of the hospital generally to see that the hospital develops as a place where all activities are directed to the patients' good.

I think it is the Ministry's intention to have the chief officer a layman. The title medical superintendent is to go and a new superintendent is to appear, the secretary superintendent, a term which the Northern Division of the Ministry of Health have adopted at the request of group secretaries. A form to this effect has been printed and has been used.

Without in any way disparaging lay administrators, I do not think that the general direction of a mental hospital should be in other than medical hands.

Who is it who wants to abolish the medical superintendent? The few lay administrators I have spoken to have said that they prefer to have a medical superintendent. I imagine that this would be the general wish of nurses and of the public generally.

A certain number of consultants seem to have suffered considerably, but the real way of dealing with the situation is surely to produce better medical superintendents, and there are two or three bodies which would doubtless be willing to undertake some form of training in medical administration, which could perhaps be offered to every consultant two years after taking up his appointment.

De la Pole Hospital, Willerby, Yorkshire. J. A. R. BICKFORD.

SIR,—Many medical superintendents are active in rethinking the relationships between mental hospital and community and many of us who ourselves are looking for a rational way to administer a mental hospital must experience that same sense of sin with which "Analyst" (Feb. 28) confronts us and must want to hide our faces.

But if a solution is to be found allowance must be made for this automatic sense of guilt. If a member of the staff of a mental hospital considers that the methods by which his organisation is being run could be improved he should not allow his feelings of loyalty to his medical superintendent to prevent him from saying so.

Many kinds of people work in the complex unit of a mental hospital. Most nursing staffs have a sense of belonging which promotes the interests of the organisation. This feeling is sometimes not shared by the ancillary staff, whose services then are perhaps not as worthwhile. Industrial organisations may achieve the "motivation" of their personnel by issuing bonuses and by profit-sharing. We have to motivate our staffs by other means to the end that they will attach a part of their egos to the hospital and feel, when they are working for the hospital, that they are working also for themselves.

I believe that there are a number of ways that this could be attempted and one of them has a bearing on the present discussion. This would be the election, to the chairmanship of the hospital management committee, of one of the consultants who would thereby be vested with powers of policy-making and executive decision-making for a period of, say, five years. At the end of each term of office, or before if he wished it, he could offer himself for re-election for another term.

The electorate would be wide-based and would consist of two colleges—one composed of the medical and nursing staff and the other of the clerical and artisan staff, the votes of the first being weighted more heavily than those of the second. In this way the consultant chosen would be likely to have the widest support, with a mandate to carry out his policies; and he would have been chosen by those with whom he had already had day-to-day dealings, who should be wiser in assessing his abilities and capabilities than a committee making a judgment at a single interview.

It appears from your correspondence columns, Sir, that there may be some medical superintendents who are excellent and efficient administrators but who cause dissension and hostility by unfortunate inter-staff-member relationships. There would probably be fewer such if they had to recognise their electorate.

The more that checks and balances are introduced into a constitution the more rigid it tends to become and I would not wish to see many checks to the power of the "director" (I think the term "superintendent" should have gone out with "asylum") except, firstly, the limitation of his term of office unless re-elected, and, secondly, his exclusion from the posts of chairman and secretary of the medical advisory committee.

It can be argued that checks, balances, and the resulting stability are desirable, but I think psychiatry is now just at the end of the first decade of a large transitional process which will go on for many more decades. A democratic, periodically elected and rigorous medical administration seems to me to be more likely to keep abreast of and give a lead to current thinking than the present system of a continuing governorship.

Purley, Surrey. H. DALE BECKETT.

SIR,—May I add a few words about the mental-hospital controversy? My colleague Dr. Bickford has, in his letter of March 14, admirably summarised the situation in England. The Scottish position has so far been left unrecorded.

In this country we have been fortunate in that mental-hospital administration has developed against a constitutional background simpler and more flexible than the English. It is probable also that the Scottish Board of Control has been less remote and more an integral and

helpful part of that administration than its English counterpart. Whatever the larger reasons, and at the risk of self-deceit, one feels that the exogenous factors said to have engendered the recent philippics do not exist in Scotland. One cannot know of personal factors and unconscious motivations but from our northern fastness their immolatory frenzy is both puzzling and alarming; it is puzzling because it is difficult to identify the typical Scots superintendent (by custom and necessity a sort of primus inter pares) with the archetypal ogres delineated; it is alarming because the abolition of superintendent's responsibilities is the deliverance of our patients into the hands of the Philistines—efficient, patient-day, index-card, three-part-introduction-form Philistines—but still Philistines.

Among my colleagues, of all grades of seniority, there is general apprehension that it is already too late to save the Scottish system from even the least political proposals of the English Bill.

If we don't, a pliable, human, and autochthonous system of control will be discarded, to be replaced by a rigid and exotic regime. And time is not with us.

Argyll and Bute Hospital, Lochgilphead, Argyll. IAIN MACCAMMOND.

IMMUNOLOGICAL REACTIONS IN THYROID DISEASE

SIR,—It may be of interest to readers of our article on complement-fixation reactions in thyroid disease (March 28) to know that the serum recorded there as "McG" was the same as that described as "serum 1" in the immediately preceding paper by Dr. Anderson and his colleagues. This serum, which gave excellent complement-fixation against both thyroglobulin and T.C.F. factor, was very kindly sent to us by Dr. Anderson and proved to be the key to a proper understanding of these reactions.

University College Hospital Medical School, London, W.C.1. G. BELYAVIN
W. R. TROTTER.

PRISON MEDICAL OFFICERS

SIR,—Permit me to comment on certain matters raised by "White Slave" in his letter of April 4.

Your correspondent would have us believe that before entering the Prison Medical Service he was deceived as to what his duties would be. I can scarcely believe this; he must have known that his work would be concerned with the general medical welfare of the prisoner—a close comparison to civilian general medical practice, together with a certain amount of psychiatry. I am sure that it is not the intention of H.M. Prison Commissioners that he should act "the role of specialist psychiatrist". What then is his complaint? If I understand him correctly it is that he is not allowed to assume the role of a psychiatric specialist within the service. But then why should he be? Of his own free choice he became a prison doctor with the duties that such a position entails; presumably he was not prevented from becoming a psychiatrist if he had so chosen.

He takes to task Dr. H. K. Snell, director of medical services of the Prison Commission, because in an address to the annual meeting of the Howard League for Penal Reform last year he stated that there remained a great need for more specialist staff in the medical service, and your correspondent has assumed that what Dr. Snell had in mind was the importation of such specialists from the National Health Service. The staff for the East-Hubert Institute, remand centres, &c., must be recruited from somewhere—where better than from psychiatrists who have undergone proper training within the National Health Service? Is it perhaps that "White Slave" feels that in open competition with such trained personnel he will stand little chance of obtaining one of these posts. Be that as it may, surely this is not a reason for allocating these positions to prison medical officers who hold a D.P.M. and who have become disillusioned with the Prison Medical Service and now want to jump on the psychiatric band-waggon. Of course it may well be that "White Slave's" original motive for joining the Prison Medical Service was the hope that it may prove to be a short cut to the top of the psychiatric tree (the big fish in the small pond); perhaps he wished to avoid that which consultant psychiatric status within the National Health Service now entails—namely, a proper basic training, including four years as a senior registrar and a higher medical qualification. There can surely be no quarrel if it is the desire of H.M. Prison Commissioners to recruit the best possible psychiatric material for these posts whether the recruitment comes from within the prison service itself or from the National Health Service.

Your correspondent states that there are medical officers in the Prison Medical Service who are qualified as psychiatrists. I am not sure what he means by this but I very much doubt whether there are many, if indeed there are any, medical officers within the Prison Medical Service who would obtain a consultant appointment in psychiatry in the National Health Service at the present time. And surely "White Slave" would agree that these psychiatric posts of the future within the prison service should be staffed by those who hold recognised consultant appointments with regional hospital boards.

It is always painful to hear of colleagues who are dissatisfied with their vocation, but I am sure that "White Slave", on reflection, would agree that it is undesirable that for this reason alone he should be given preferential treatment over professional colleagues with better qualifications, training, and experience.

CONSULTANT PSYCHIATRIST.

ALDOSTERONE EXCRETION IN NORMAL PREGNANCY AND PRE-ECLAMPSIA

SIR,—We hasten to reply to the letter of Mr. Sophian (March 28) because the "dilemma" to which he refers is the result of a misunderstanding. In quoting from the discussion of our paper he has attributed to us a single hypothesis which he has formulated by combining statements from alternative hypotheses.

We offered as *one* possible explanation of the lowered intracellular sodium in normal pregnancy the aldosterone effect observed in mice by Woodbury and Koch. It should not be inferred that we hold that aldosterone is responsible for this change in pregnancy. In fact our implication was to the contrary, because this theory fails to account for the high intracellular sodium in pre-eclampsia.

The *second* hypothesis calls for an opposite view—namely, that some other factor in pregnancy is responsible for the lowering of intracellular sodium. Such a change could provide the stimulus to aldosterone secretion, especially if one of the effects of this hormone is to increase intracellular sodium. Pregnancy may proceed normally with these two opposing forces in balance. A decrease in the cell-sodium-lowering factor (C.S.L.) might then precipitate pre-eclampsia.

As to the origin of the hypothetical C.S.L. factor, we have indicated only that the placenta is a possible source. Scientists have sought the ætiological basis of pre-eclampsia for many years. Hypotheses are intended to facilitate the design of experiments. We will welcome any factual evidence that casts light on the problem, but we cannot accept the suggestion that our second hypothesis can be dismissed after "a little reflection".

Toronto. D. KUMAR
L. A. W. FELTHAM
A. G. GORNALL.

FATAL TUBERCULOSIS IN A GENERAL HOSPITAL

SIR,—Dr. Warren Browne's letter of March 28 suggests that a much wider investigation for sources of tuberculosis is necessary than is sometimes appreciated. A recent experience in this hospital confirms this view.

In September, 1958, a boy was admitted with miliary tuberculosis. On X-ray examination his sister, aged 3½, was found to have a primary tuberculous chest lesion, but no source of infection could be discovered in the immediate family or environment.

It was only when the paternal grandparents were examined, in Holland, as a result of our inquiries, that the grandfather was found to have open tuberculosis, for which he has now received treatment. He was visiting his son's family at the approximate time the children contracted their illnesses and no other source of infection has been found.

I feel that this is an interesting case of "long-range" contact tracing, which in these days of ease of travelling gains some significance in the epidemiology of disease.

Bristol Royal Hospital for Sick Children. C. W. JENKINS.

PSYCHOSOMATIC DISORDERS IN CHILDREN

SIR,—I am grateful to Dr. Apley for his excellent paper on psychosomatic disorders (March 28) which brings me nearer to recognising the term psychosomatic as applying to a conception of illness rather than to particular disorders.

He mentions that for non-specialists "treatment involves taking a personal interest, not limiting ourselves to the superficial, listening patiently, explaining and reassuring, and offering sensible guidance". In another place he rightly warns that reassurance which does not reassure is a waste of time.

It seems to me that there is a need for a particular assurance for some patients which is only too often overlooked, with consequent prolonging or worsening of the patient's illness. The patient suffering from a physical manifestation associated with a hidden emotional disturbance is often quite hopeless about the emotional situation. Perhaps this is why the emotional disturbance has to be hidden. Hopelessness of this sort has been clearly demonstrated to me several times recently.

On one occasion the patient was a young man with abdominal discomfort, very like that due to a stomach ulcer. He had had similar symptoms some months before and there was a note to say that he was acutely upset over a girl friend. On the second occasion he assumed a cheerful aspect which seemed somehow rather brittle. When pressed he averred that he had "quite given up" worrying about girls. This point was taken up with him and the doctor said something like this: "Then it may be that your physical pain is a direct substitute for the emotional pain which you refuse." He did not appear to lose his poise but said after a little consideration, "Then what hope is there?"

This question brought home to me that one of the first things the patient needs, perhaps even before he is faced with his emotional problem, is some sort of assurance that many of us come to believe, rather wrongly, that emotional problems are insoluble.

As a corollary, if the doctor adopts this attitude he must also be prepared to tolerate with the patient enough emotional distress to give the patient practical proof of his, the doctor's, statement that emotional distress is tolerable.

Another patient, a girl, after referral to an orthopædic surgeon for pain in the knees, was sent back with the comment: "Consider this an emotional disturbance." When the girl then returned to her doctor she, having hitherto been a cool, calm, and collected girl, was nearly in tears. "He thought I was just silly," she said. It needed a very brisk retort from her doctor, "It's not silly to be miserable", to make her begin to see the impossible position which she had quite unnecessarily created for herself, over many years, with regard to her emotions.

Similarly with a young married girl scared almost out of her wits over accepting sexual penetration: although it is well known that it is not enough to examine and to reassure about the fear that she is "not like other girls", "much too small for intercourse", it is sometimes not so clearly seen that there is an immense hopeless fear of being a little girl. What may be most needed, as a beginning, is the assurance that this situation is understood and accepted by the doctor with the confident knowledge that there is still plenty of time to grow up. Then an exploration of the lag in emotional development can be begun.

University Health Service, Bristol. AGNES WILKINSON.

SIR,—Dr. Apley stated that "allergic or infective stresses are less likely to produce asthma, or may completely fail to produce it, when the patient is emotionally stable".

Miller (allergist) and Baruch (psychotherapist) feel that "allergic symptoms express hostility, mask a feeling of guilt or anxiety, and at the same time represent attempts to gain sympathy".

Some years ago an asthmatic girl of 8 was referred to me for hypnotherapy. Her sister, aged 16, had suffered from asthma from the age of 4 and died. Four weeks later the younger one developed it. The father stated that although the two children were fond of each other they often had violent quarrels.

Under hypnosis I questioned the child and got a confession that she felt guilty of her elder sister's death. As she was a very intelligent child it was not a simple matter to convince her that she was completely innocent, and it was only when I felt she was reassured that I permitted her to awake from the trance.

She lost her symptoms, but I would hate to think what would have happened to her had she gone on year after year being treated for allergy.

London, W.1. A. P. MAGONET.

THE RIGHT KIND OF CONTROL

SIR,—Your annotation of March 21 refers to an experiment of ours on the influence of physical side-effects in drug trials, and comments that "unfortunately since the urines were not tested for the drug we cannot be sure that all the treated patients took their capsules, or at least the right ones". In the context of the Rome proceedings,[2] it may not have been made sufficiently clear that this point is irrelevant to our argument, but a fuller account of our findings has now been submitted for publication.

We were not concerned to show simply that nurses often fail to recognise side-effects, or that patients often fail to take their medicine, both of which may be accepted as true. We were interested in what happens when physical side-effects *are* observed. Our main findings were, first, that a specific drug-induced sign (in this case, flushing) was reported in patients not receiving the drug at all, and secondly, that other symptoms (which cannot be ascribed to the drug) were reported much more frequently in patients who had already been observed to show this sign. We suggested, therefore, that the occurrence of physical side-effects of treatment may influence

1. Miller, H., Baruch, D. W. The Practice of Psychosomatic Medicine as Illustrated in Allergy. New York, 1956.
2. Mayer-Gross, W., Harris, A. D., Letemendia, F. Proceedings of the First International Congress of Neuro-psycho-pharmacology, Rome (in the press).

subsequent reporting by directing attention both to the particular sign or symptom already observed, and to the patients who have shown it. These results certainly lend support to your plea for caution in interpreting double-blind trials, and for further empirical testing of trial methods.

Department of Experimental Psychiatry, University of Birmingham. F. LETEMENDIA A. D. HARRIS.

SPRAY-PACK THERAPY IN DERMATOLOGY

SIR,—I was interested to read Dr. Hodgson-Jones' letter of March 28. Some of my patients also experienced a severe burning sensation when the earlier sprays containing isopropanol as diluent were used and a few would not continue to apply them.

With the spray now marketed [1] my patients report freedom from burning or stinging even when the treated areas are acutely inflamed. Providing the instructions are followed the spray has proved extremely economical when used in the treatment of large areas of eczema. Its use, however, must be strictly limited to non-infected skin lesions, but in the presence of even mild skin sepsis its application is likely to be followed by an acute flare-up of the eruption.

I consider that in moist eczema it is far safer to use an application containing both hydrocortisone and either an antibiotic or a bacteriostatic compound. This relatively new and harmless diluent opens up many possibilities for the development of other propellant sprays designed for the speedy and safe control of moist infected eczemas and dermatitis.

London, W.1. NAPIER THORNE.

A REMEDY FOR AGEING?

SIR,—Your restrained and judicious annotation (March 14) on the new Roumanian "wonder drug" omits to mention that a considerable amount of work on the systemic use of procaine was done at an earlier date in this country. Whereas the Roumanian work is, you tell us, purely anecdotal, the work done in Britain suggests a possible rationale, and also, unfortunately for those who seek a cure, a likely limitation.

The work of Ungar [2] led me to hope that procaine might stimulate the output of corticotrophin and so of hydrocortisone in patients with rheumatoid arthritis, and in 1946 I began treating patients with intravenous procaine hydrochloride. The results, which were moderately good for those days, were reported to the Section of Physical Medicine of the Royal Society of Medicine.[2] Both corticotrophin and procaine hydrochloride usually caused, when the treatment was successful, the disappearance from the blood of the substance called by Ungar "splenin B" and the appearance, when it had previously been absent, of "splenin A". Splenin A, invariably found in healthy people,[2-6] decreases the bleeding-time of guineapigs.[2 4 5 7] Splenin B, which has the opposite effect, has not been reported in the blood of healthy people, but has been found in that of patients suffering from active rheumatoid arthritis, spondylitis, acute rheumatism, non-articular rheumatism, thyrotoxicosis, scurvy, and various hæmorrhagic states.

The advent of readily available corticotrophin and cortisone caused me temporarily to lose interest in procaine, for it seemed likely that these substances did the same thing more effectively. My use of intravenous procaine in a number of conditions known to be susceptible to corticotrophin has hitherto strengthened this view. It has, however, never been finally established that procaine works by stimulating the output of corticotrophin and it would be worth while to make sure about this. Ten years ago the biochemical methods were not good enough.

If indeed procaine works only because it stimulates the production of corticotrophin, the remarks of Max Reiss [8] about the general effects of corticotrophin in patients with involutional melancholia become relevant. "In every case the skin began to look and feel to the touch more supple and thicker . . . the hair of the head regained its lustre, losing some of its dry, brittle quality". Would therapeutic optimists call this rejuvenation?

It seems clear that further research on the pharmacology of procaine hydrochloride is needed. In the meantime it would appear to those who have used it to be merely a mild activator of the pituitary-adrenal system and certainly no panacea. Efforts by the lay press to "sell" it as such show a serious lack of responsibility.

London, W.1. RAYMOND GREENE.

1. 'Cortril', Pfizer.
2. Ungar, G. *J. Physiol.* 1944, **103**, 333.
3. Greene, R. *Proc. R. Soc. Med.* 1950, **43**, 16.
4. Ungar, G. *Endocrinology*, 1945, **37**, 329.
5. Ungar, G. Personal communication, 1947. Quoted in ref. 3.
6. Bergel, F. Personal communication, 1947. Quoted in ref. 3.
7. Greene, R., Vaughan-Morgan, J., Gammon, J. *Brit. med. J.* 1952, i, 17.
8. Reiss, M. *Proc. R. Soc. Med.* 1950, **43**, 19.

SOFT DRINKS

SIR,—I note that Dr. Franklin Bicknell (March 14) seems very worried about "cola" drinks, especially as certain of the syrups (I imagine he spoke primarily of 'Coca Cola') are imported from the United States and their ingredients are secret. Actually this is not true because the formulæ of these various cola drinks have been disclosed to the Food and Drug Administration of the Department of Health, Education, and Welfare on many occasions. The only "drug" which is in cola drinks is caffeine. If Dr. Bicknell would look in the *Federal Register* of Dec. 9, 1958 (23, R. R. 9511, p. 2), he would find that cola drinks contain from $\frac{1}{3}$ to $\frac{1}{2}$ grain of caffeine in a six-ounce bottle of the drink. I would feel that Dr. Bicknell could sleep soundly at night.

State University of New York, Brooklyn, New York. PERRIN H. LONG.

PSYCHIATRIC SEMINARS FOR GENERAL PRACTITIONERS

SIR,—I read with concern Dr. Lask's letter of March 21 about the refusal of the British Postgraduate Medical Federation to give official recognition to the Tavistock Clinic seminars for general practitioners. Dr. Lask will, I am sure, be interested to know that postgraduate psychiatric training precisely along the lines he mentions has been in existence at the department of child and family psychiatry of the Ipswich group hospitals for many years. The Tavistock Clinic is not alone in this important field.

Under Dr. J. G. Howells' guidance, fortnightly seminars for G.P.s were started in 1950; an annual five-day course for G.P.s, psychiatrists, and public-health medical officers has been in existence for six years; a fortnightly discussion group of six G.P.s is now in its second year, and a second group is shortly to be formed. In addition regular courses are held for district nurses, health visitors, &c.

The most recent annual course has just ended, being attended by 42 doctors from diverse spheres of medicine and from diverse places as far apart as Scotland, Wales, and the Isle of Wight. This year the G.P.s more than held their own not only numerically but also in their contributions to the discussions, formal "teaching" being kept to a minimum.

It is encouraging to find that the annual course was, this year, recognised by Cambridge University Medical School for the purpose of grants under the Ministry scheme for G.P.s, and was indeed formally opened by Prof. J. S. Mitchell, regius professor of physic at the University. The imaginative attitude of the regional hospital board received a sympathetic response from the University, and all concerned are to be congratulated on their initiative. Their helpful attitude is perhaps partly rewarded by the resounding success of the course, which

received unanimous praise not only for its content but also for the enthusiasm and humanitarian approach of all members of the department, who offered us not only discussions but also an opportunity to see all facets of the department including psychometrics and play diagnosis and therapy.

Clearly we in East Anglia are more fortunate than our colleagues in London and are, in medical matters at least, not quite so " retarded " as is sometimes supposed! May one hope that others may soon follow the example of our regional hospital board and ancient but progressive University?

Stowmarket, Suffolk. HENRY A. FRASER.

EFFECTIVE USE OF TEACHING TIME

SIR,—Mr. Chard's interesting letter of March 28 enquires whether spare-time reading has any value at all. Unfortunately, our experiments give no evidence on this point, as the amount of spare time so spent was selected by each student for himself. The 21-hour student might have done much worse if he had done no spare-time work, and the 0-hour student might have done better if he had worked longer. The converse might even be true, and the 21-hour student might have done better by reading less. There are difficulties in allocating fixed numbers of hours of spare-time work to different students, and ensuring that the specified number of hours of work is done by each student with the same competence as would be shown spontaneously. At present we can only suggest that Mr. Chard tries different amounts of spare-time work with adequate experimental design and testing: he may then find his own solution to the problem.

Department of Pharmacology, The London Hospital Medical College, London, E.1. C. R. B. JOYCE
M. WEATHERALL.

OBSTETRICS AS A DISCIPLINE

SIR,—Professor Claye (Feb. 7) states that the doctor and not the midwife should give comfort and advice to the patient. He disagrees with the Ministry of Health report urging that private interviews be arranged between midwife and patient in hospitals. As a midwife, may I make three comments:

(1) There are some things a mother will ask another woman but not a man.

(2) Most women don't like to ask a doctor what they feel he may think is a " silly " question and be made to look a fool; but it is this " silly " question which is often the one which is really worrying her.

(3) Many patients don't like to " bother the doctor " because they feel he is so busy—but they will unburden themselves to a midwife, whose time, they feel, is not so important as the doctor's.

Bulawayo, Southern Rhodesia. N. C. DODS.

THE CHROMOSOMES OF MAN

SIR,—I read your leading article of April 4 with great interest. You seem, however, to have fallen into a trap which may well deceive others. You write: " Is an XXY a female with an extra Y, or a male with an extra X: is an XO a male with lost Y, or a female with lost X? There may well be answers to these questions (sex ratios of sibships might provide it)." You are presumably suggesting that if an XXY is a female with an extra Y, she will on the average have more brothers than sisters in order to produce a sex ratio near unity in the whole sibship. This argument is mistaken since it ignores the fact that these sibships are selected because they contain an XXY propositus, and will therefore be expected to have more females than males if the propositi are counted as female. The sex ratio among the siblings of the propositus should be the same as that in the general population whatever his or her " real " sex, since the sex of the siblings is determined independently of that of the propositus.

Department of Social and Preventive Medicine, University of Manchester. M. G. BULMER.

*** Dr. Bulmer may well be right. We have heard discordant opinions on the matter and would be glad to be assured that this is the correct answer. But surely something can be learnt from sibship sex ratiós—for example, in testicular feminisation where, even though the question of the sex of the propositus leaves a margin of error, the broad conclusion that the cases are feminised males is unchallenged. Is it only in such extreme cases that the ratio means anything?—ED. L.

NEEDLE IMPLANTATION OF YTTRIUM SEEDS FOR PITUITARY ABLATION

SIR,—We wish to thank Mr. Fergusson and Dr. Stevenson, and Mr. Small (March 21) for their interesting comments on our paper.

The claim by Mr. Small that of his 100 patients surgically hypophysectomised for metastasising breast cancer, 24% obtained disappearance and healing of all deposits, and that only 1 has died of cancer over a period of study of $3^3/_4$ years, is surprising, for this claim exceeds that of published series quoted in our paper. A possible explanation of the long survivals would be that the cases were hypophysectomised at an earlier stage than in the other series. Without a statement of the survival of his non-responders, it is impossible to assess the effect of the operation. It would be interesting to hear how often he finds bone deposits " disappear and heal ".

We are also surprised at his statement that tests of pituitary function are difficult to assess, and that " assumption from other glandular functions are most unsatisfactory ". We wonder how he assesses the completeness of his own hypophysectomies, apart from the effect on the tumour. We have found that this latter yardstick is not necessarily related to the degree of impairment of pituitary function. In fact, one of our patients had a clear recession of her bone deposits on clinical radiological, hæmatological, and calcium-metabolism studies after each of 3 implants into the pituitary: the first 2 implants produced no evidence of hypopituitarism.

Mr. Small also states that " surgical removal . . . is the most likely method of obtaining full recession of tumour . . . "

On what evidence? Until proof of hypopituitarism is produced, the completeness of any type of pituitary ablation is in doubt. We had not wished to discuss tumour response in detail before our small series was enlarged, but felt that our overall remission-rate of about 50% was worth quoting, since it is comparable to the results of other reported surgical series. Our longest remission is 3 years. In comparing two methods, not only must the stage of carcinomatosis be quoted and found comparable but also mortality and morbidity from the procedure. Mr. Small would like to operate on the non-responders to implantation, and also when the responders relapse. Very few of our patients could be considered a reasonable surgical risk for craniotomy, whereas further needle implantation has been, to date, entirely without difficulty or complication. Does Mr. Small reoperate, or is his excision so complete that failure to produce hypopituitarism is unknown?

We submit that our data have shown that properly implanted yttrium-90 seeds can produce functional hypophysectomy, and as good an effect on that cancer as the published surgical results.

RUSSELL FRASER
G. F. JOPLIN
J. W. LAWS
R. MORRISON
R. E. STEINER.

Hammersmith Hospital, London, W.12.

BRITISH ASSOCIATION OF THE HARD OF HEARING

SIR,—As president of the British Association of the Hard of Hearing, may I draw the attention of your readers to the excellent help that it is able to give to patients who suffer from a chronic impairment of hearing that is found not to be amenable to medical or surgical treatment.

The clubs, at which new members are warmly welcomed, are provided by different branches of the Association. Social evenings are regularly held. There are classes for deafened adults to help them to acquire skill in using hearing-aids and in lip-reading. Frequently there is a youth section for young men and women who have not been able to find opportunities for enough social life elsewhere.

My wife and I, through long experience in the University of Manchester of holding evening classes and informal meetings for adults who have suffered a partial or total loss of hearing, know how much help can be given to them both occupationally and socially. The clubs help these people to learn to live with their deafness. Persons suffering from a total loss of hearing are always sure of an understanding welcome in the clubs of the Association.

It has been noted, and we have observed it to be true, that a progressive loss of hearing in later middle age is liable to be a source of much unhappiness and mental stress.

The resources of the British Association of the Hard of Hearing, its officers and members are available to help all people for whom loneliness and anxiety have become a consequence of deafness.

The honorary secretary, Mr. C. H. Mardell (The British Association of the Hard of Hearing, Briarfield, Syke Ings, Iver, Buckinghamshire), will be glad to send to anyone who is interested the address of the nearest branch of the Association.

Department of Education of the Deaf,
The University, Manchester. A. W. G. EWING.

DEATH FROM TONSILLECTOMY

SIR,—In his outspoken article of March 28, Dr. M. E. N. Smith asks whether complete investigation of the blood in all cases should be mandatory. May I suggest that routine preoperative blood investigation would probably reduce the number of tonsillectomy deaths due to bleeding, which recur with tragic regularity (perhaps a death once every five years) in all hospitals where this kind of work is undertaken.

Complete blood investigation would be unnecessary and time-consuming, but routine hæmoglobin estimation, white count, differential, and film report would exclude anæmia, leukæmia, and platelet deficiency; a clotting-time and bleeding-time would exclude hæmophilia and von Willebrand's disease in their active phases. It is uncertain whether these conditions often cause postoperative bleeding but undoubtedly they may do so.

Even if lack of laboratory facilities precludes so detailed an examination in all cases, the clinician should inquire for any family or past history of bleeding diathesis; patients with such a history should have a full investigation before operation. In other cases perhaps a routine bleeding-time should be done before operation (a simple test needing no special apparatus or skill) and this would exclude von Willebrand's disease in its active phase.

Two recent occurrences illustrate the point.

A boy of 7 who had severe post-tonsillectomy bleeding necessitating transfusion was found at subsequent investigation to have von Willebrand's disease (hereditary pseudohæmophilia; constitutional thrombopathy; hereditary capillary purpura). The disease is characterised by alternating bleeding and normal phases: a prolongation of the bleeding-time is found when the disease is in the bleeding phase; at other times the test is normal and surgery may safely be undertaken.[1] If, however, the bleeding-time is prolonged, operation should be postponed.

A boy of 5 with a hæmorrhagic history was sent by a dental surgeon for blood investigation before teeth extraction. He was found to have von Willebrand's disease. He attended the laboratory once a week for a bleeding-time test; when this was found to be normal he was admitted to hospital the same day; an hour before operation the bleeding-time was again found to be normal; the teeth were extracted without any abnormal bleeding.

I wish to thank Mr. P. C. Rushton and Mr. H. Robinson for permission to cite cases.

Pathology Department,
Worthing Hospital. R. AIDIN.

ŒSOPHAGEAL SPASM

SIR,—I should like to draw attention to a condition which is sometimes mistaken for coronary disease—an acute attack of substernal pain radiating to the lower jaw, not the arms, due to spasm of the lower end of the œsophagus. It usually occurs in neurotics and the attacks may be very infrequent. After swallowing or drinking a glass of water, the patient feels the spasm relaxing and the pain vanishes—a simple differential test.

London, W.1. M. W. BROWDY.

CARDIORESPIRATORY SYNDROME OF EXTREME OBESITY

SIR,—The cardiorespiratory syndrome of extreme obesity may be Pickwickian, but the applicability of this title is questioned in Dr. Berlyne's case-report,[2] while its use is defended by Dr. Bass.[3] The article by Burwell et al.[4] makes it clear that, in originating the term Pickwickian, they had in mind the Fat Boy, Mr. Wardle's Joe, and not Mr. Pickwick himself.

Fat Joe, however, had already been taken as typical of another syndrome: in the discussion of Fröhlich's syndrome in Boyd's *Pathology*, Joe was used as an example, perhaps testifying to his widespread appeal, despite his drawbacks. It seems that he will have to remain an endocrine problem.

A case-report in the *New England Journal of Medicine* [5] promoted some discussion [6] of this eponymic matter. Simpson [7] noted that Dr. John Fothergill, of London, had published a description of two patients with this disorder prior to 1781. Simpson thus disposed of Samuel Pickwick and Fat Joe in this regard, but did not propose "Fothergill's syndrome"; and the scientific search for a suitable eponym can continue.

Buffalo, New York. ROBERT D. BUSIEK.

PSYCHOANALYTICAL TREATMENT

SIR,—Very few patients in my practice are referred for consultant psychiatric opinion. Of this small number, perhaps only one or two each year are found by the consultant to need analytical treatment. However, this is as far as things go, for, at any rate in Central London, it appears to be virtually impossible to obtain analytical treatment for patients within the National Health Service. It is, on the other hand, extremely easy if the patient has financial means. I should welcome suggestions.

London, S.W.1. BENJAMIN LEE.

1. Whitby, L. E. H., Britton, C. J. C. Disorders of the Blood; p. 398. London, 1957.
2. Berlyne, G. M. *Lancet*, 1958, ii, 939.
3. Bass, B. H. *ibid.* p. 1019.
4. Burwell, C. S., Robin, E. D., Whaley, R. D., Bichelmann, A. G. *Amer. J. Med.* 1956, **21**, 811.
5. *New Engl. J. Med.* 1957, **257**, 1227.
6. Busiek, R. D. *ibid.* 1958, **258**, 1020.
7. Simpson, H. N. *ibid.* 1958, **259**, 34.

Obituary

ROBERT MUIR

Kt, M.D. Edin., D.C.L., LL.D., Sc.D., F.R.C.P., F.R.C.P.E., F.R.F.P.S., F.R.S.

Sir Robert Muir left his chair over twenty years ago; but his work as scientist, teacher, and writer, and his qualities as a mentor and friend, have ensured that for many people the Glasgow school of pathology still means Bobby Muir. Today over 20 of his pupils hold chairs in different parts of the world; new editions of his textbooks are still studied in medical schools at home and abroad; and his own pioneer contributions to immunology, hæmatology, and malignancy are part of the accepted body of knowledge of his specialty.

Press Portrait Bureau

He was born in 1864 in his father's manse at Balfron in Stirlingshire. A few weeks later the family moved to Hawick, and he was educated at the Academy there and at Edinburgh University. In 1888 he graduated M.B. with first-class honours, and with a Vans Dunlop Scholarship began his career as a research-worker in the department of pathology under Professor Greenfield. In 1890 he obtained his M.D. with a thesis on the reaction of leucocytes in disease for which he was awarded a gold medal. Two years later he was appointed senior assistant to Greenfield and pathologist to the Edinburgh Royal Infirmary. When a lectureship in pathological bacteriology was created in Edinburgh he was the inevitable choice as its first holder. In 1898 he moved to St. Andrews to become the first professor of pathology there, but he held this post for only a year before he was offered the chair at Glasgow. He was also appointed pathologist to the Western Infirmary, and much of his research was carried out in its pathological institute.

To these early years in Glasgow belong the important investigations which were published in 1909 as *Studies on Immunity*. From this work sprang his later research with Shaw Dunn on iron storage, with McNee on jaundice, and with Cappell on the reticuloendothelial system. Before he left Edinburgh Muir had already published, with Ritchie, the *Manual of Bacteriology*. Beginners and experts alike soon found it indispensable. Its soundness became proverbial, and to quote from it was to silence criticism. His own *Textbook of Pathology* was first published in 1924 and is still renewed in successive editions which are now supervised by Muir's successors in chair and laboratory. To an American who seemed to be laying too much importance to the length of a colleague's publication list, Muir once gently remarked, "Ah, in this country we judge more by its weight." Even by his own criterion Muir's publication list will not be found wanting.

He met new advances in his spreading specialty with discriminating hospitality, and he considered that the recognition of what was really of fundamental importance was the teacher's most difficult task. In his own classroom and laboratory he was insistent that the centre of study should be the disease—"neither merely the particular bacterium or virus on the one hand, nor merely the tissue damage and reaction on the other".

He was the least pompous of men, but even his reluctance and modesty could not evade all the honours which his colleagues and friends were anxious to give him. He was elected F.R.S. in 1911. He was a fellow of the Royal Colleges of Physicians of London and of Edinburgh, and of the Royal Faculty of Physicians and Surgeons of Glasgow. He was created a knight in 1934. He held honorary degrees from several universities. He was awarded a Royal medal by the Royal Society and a Lister medal by the Royal College of Surgeons of England. This last was the first award to anyone who was not a surgeon, and in delivering his Lister lecture on malignancy Muir modestly described himself to the college as "in some sort a layman".

After he retired from his Glasgow chair in 1936, he settled in Edinburgh—where he spent many years of vigorous retirement. Less than five years ago, when already 90, he made a trip to Australia to visit an older sister, and a friend described his bearing there as that of a "youngster of 70". He died on March 30 at the age of 94.

D. F. C. writes:

"Bobbie Muir had in a remarkable degree the quality of inspiring in his students, his staff, and his colleagues an affectionate regard that his many little eccentricities did nothing to diminish. He was a man of great charm and of simple tastes; he hated cant and humbug and had no patience with pomposity or pretentiousness of any kind. His outstanding integrity and honesty won for him immense influence in medical affairs, but he had no lust for power and always used his influence sparingly, to the admiration and respect of his contemporaries.

"In his earlier years in Glasgow he was greatly preoccupied with establishing firmly the independence of the discipline of pathology. In research, he had the almost intuitive knack of going at once to the heart of the problem and in this work he gathered around him a remarkable band of disciples, most of whom later attained to high academic office. Indeed it is true to say that no other man has ever filled with his own pupils so many academic chairs of pathology and bacteriology.

"In his earlier years he appeared to his juniors a somewhat aloof and masterful figure of great authority of whom they stood much in awe, a fact that he could never understand and found difficult to accept. This was largely due to his own shyness and the restraints imposed by the somewhat formal atmosphere of academic life in those days. When, after the 1914-18 war, much of this formalism disappeared no-one could have joined more happily the younger members of his staff on the golf course or on fishing expeditions. Golf and fishing were his principal hobbies latterly, and he was insistent that work and intellectual pursuits alone were not enough."

J. F. H., who was Muir's assistant and lecturer for the last six years of his office, recalls his methods in the laboratory:

"In animal experiment he would outline what we would do, pause for comment, but refrain from discussion until all results were available and had been repeated, by which time discussion would be minimal and conclusions clear and brief. When I once ventured to remark apropos of his dictated report on a section, that the surgeon would prefer something more definite, he lisped, 'Experience makes me more and more unwilling to give an opinion in a matter of doubt.'

"He was known far beyond his adopted university town,

and when, on the award of the gold medal of the Royal Society, it was decided to present him with his portrait in oils by Fiddes Watt, subscriptions reached us from the Americas, the Antipodes, Egypt, South Africa, and Japan, and were such that a bust by Paulin was easily possible. This was a happy addition, because it shows us more of the man we knew, and the class medal prepared from it will mark the affection and esteem with which generations of students regarded him."

On Muir's 70th birthday a score of his former students, more than half of them by then professors, contributed to a *Festschrift* in his honour. J. W. H. describes some of the qualities which inspired this tribute:

"Muir would give almost any sincere applicant a few feet of bench space in the department. If the man turned out 'not good enough' he would not stay for long; but if he proved to be 'all right' he became one of the family—and so remained. In short, Muir's attitude to the selection of juniors for training was essentially personal and empirical. Who could finally judge a man at a short interview? True, there might be favourable indications: the man might show signs of life, of humour, or of unusual understanding and knowledge; or—more reliably—he might show interest in talk of fishing or golf. But the real selection was made by taking the man on some temporary basis, telling him to use his freedom, and awaiting the results. Muir would not put a man on to a research problem as one might set a hen on eggs; he knew that people worked best at problems of their own choosing and if a man could not find one to interest him and make it yield something it was clear evidence that he was 'not good enough'. But once a man had picked his line of work and made some progress in it, Muir would help with all that he could give—and he had much to give, for he was a man of wide reading, high intelligence, judicial insight, and active interest. Only the hardy ones survived this kind of training, but Muir saw nothing wrong with that.

"The survivors, of course, were individuals in their own right and therefore differed widely from each other in personality and points of view. This often made for excitement and even conflict within the department. Muir undoubtedly knew more about such controversies than he often allowed to become apparent. If he intervened, his intervention would be minimal and discreet. He rightly accepted signs of difference as signs of life. After all, these men were likely to become heads of their own departments one day and it was inevitable that they should rub each other up a bit. Muir could easily afford such an attitude, for no matter how his staff might differ among themselves their loyalty to Muir himself was absolute and their personal affection for him was sincere and steady. It was the unifying force of a lively department and a natural response to the air of freedom.

"A high proportion of Muir's staff and associates became professors—not because he went out of his way to push them, but because the method of selection ensured that all his men had at least some qualities to recommend them. Muir gave advice about appointments only if he was asked for it; and he possessed great insight into character and an almost instinctive awareness of who would best fill a particular post. He did not by any means invariably recommend one of his own men; he cared too much for the rightness of things, and this was what made his opinion so greatly sought and valued.

"The world of pathology is filled with legends about him—some so astonishing that they must seem like made-up tales. But there was never any need to invent legends about Muir: his daily acts and words provided enough to fill a book. I did not know him until he was 68 years old, and my most intimate contacts with him were made on the golf course. He knew and loved this game and played it with skill, judgment, and a touch of bravado under pressure designed to neutralise any psychological advantage that might be temporarily enjoyed by a man whose youth allowed him to hit a longer drive. After lunch in the clubhouse at Prestwick one day, he said to me: 'Try this chair; it's the most comfortable in the world.' Thereupon he occupied this seat himself and at once vanished into his thoughts. Some twenty minutes later he looked round and saw me. Then he looked out of the window and said: 'Ah yes! Now, if *you* have meditated sufficiently, we'll have a round of golf.' He had a great liking for life—not for parts of it only but for the whole of it as he came face to face with it. It was characteristic of him that soon after his 91st birthday he went fishing and actually hooked a salmon. With the help of good and skilful friends he landed it and enjoyed as fully as ever an experience that had so often given him pleasure in earlier days.

"No words can put Robert Muir on paper. His ability to select a good research problem was equalled only by his capacity for summarising its essentials and sensing at which point it should be attacked. His judgment was ripe and generous, but it was true and fearless. His leadership was for those whom he thought worth leading, but these he served as their best interests required.

"His tastes in the arts were cultivated and wide, and his criticism of pictures and music was especially discriminating. His understanding of people was such that he was not often deceived; but his respect for people as individuals was so real and genuine that the warmth of his spirit lives on in many hearts."

FRANCES CHARLOTTE NAISH

M.A., M.D. Cantab.

Dr. Charlotte Naish (Mrs. Edwards), who died on March 24, was a specialist in family practice, and her own experience as a mother was the practical basis of her studies on breastfeeding and child care.

She was brought up in Sheffield where her father Prof. A. E. Naish and her mother Dr. Lucy Naish both held appointments at the university before they retired to their present home in Anglesey. She studied medicine at Cambridge and at the London School of Medicine for Women, qualifying in 1933. After holding a Mabel Webb and A. M. Bird research fellowship and an obstetrical assistantship at the Royal Free Hospital she practised for a time in North London. Towards the end of the late war she moved to York and in 1948 she published the monograph on breastfeeding, based on her M.D. thesis, for which she was awarded the Hastings prize. Under the National Health Service she continued to apply her own ideas on the medical care of the family as a whole, and she described in our columns (*Lancet*, 1954, i, 1342) some of the extras—such as antenatal and postnatal clinics, relaxation classes, a mother-father club, birth control advice—which were offered in her practice. Soon afterwards she retired from general practice, and with her husband began a new venture by opening a family school in the Cumberland countryside to which they welcomed physically handicapped children.

C. D. H., who worked with her in York, writes:

"From the time Charlotte Naish joined our practice until the time she left to concentrate on mothers and babies we enjoyed a most contented and happy partnership in which she was a keen, hard worker with a great enthusiasm for everything she undertook—housekeeping, odd jobs including joinery, washing and maintaining her car, looking after her family, and doing her full share in a very busy practice. Despite all the extra work imposed by war-time conditions she found time to do research into breastfeeding. Her enthusiasm for breastfeeding was unbounded and that enthusiasm communicated to her patients always seemed to produce the most satisfactory results. She always maintained that the father should play a large part in the family unit and, as part of the infant welfare clinic, she ran an evening fathers' and mothers' club. She often travelled in the country giving lectures on her favourite subject, but though she might arrive home in the small hours of the morning, she always turned up for her daily work apparently

as fresh as ever—perhaps she drove herself too hard. After joining our partnership a third daughter was born and she later adopted two boys. She used to say that her children taught her so much and helped her to make a success of what really became her specialty."

Another colleague, M. G., writes:

"Charlotte Naish's book on breastfeeding combined knowledge gained from personal experience with much learned from close observation of many patients. It deserves its lasting reputation for the balance with which it is written (though she strongly advocates breastfeeding she emphasises that 'the most important thing is to feed the child') and for its description of the mind of the mother—'her easy tears, her easy anxieties' and the 'healing qualities of a sense of achievement'. Charlotte Naish was one of those fortunate women who use to the full their capabilities both in professional and in domestic life. In this synthesis which was inherent in her personality her maternal self overflowed into her medical work, and her family came to extend to a houseful of spastic and other children in need of her warming affection as well as of her medical care."

D.W.S., who worked with her as a trainee and later as a partner, writes:

"Charlotte Naish welcomed the visits of students and the coming of trainee assistants to her practice. She was an inspiring teacher and many a young doctor went away with a vision of the scope that general practice offers in return for enterprise and enthusiasm. She regarded her patients as people who had come with a personal problem to ask her help, and she interpreted her duty towards them in a spirit which took no account of the cost to herself. If it was clinical skill they required, they got it in good measure; if the need was a holiday for a family who could not afford it, they were loaned a car or a holiday cottage with transport provided; the old lady whose trouble was loneliness was taken out on the morning visiting round and entertained by humorous conversation; the child whose mother had died suddenly was taken into the bosom of Charlotte's own family and mothered there until satisfactory arrangements could be made.

"She said of herself that one side of her tongue was smooth and the other side rough; the ingenuous saw only the rough side and her impulsive flares of temper. In committee work as in everyday life her support was forthright for the causes in which she believed and for integrity in public affairs. She saw at once to the heart of a matter, and was gifted with a forward-looking mind.

"As a woman, she was well built and most attractive to look at. Her five children were her joy and she held their interests deeply at heart. She was very proud of her competence in the domestic arts, and indeed it was an education to the onlooker to watch her training her daughters in pastry cooking or household management. She would start out on an evening's discussion of practice affairs with a shapeless piece of material on her knee; deftly snipping and stitching as she talked, she had produced a finished blouse for one of the children by supper time! The family way of life was extremely simple with early rising and a high regard for orderliness and punctuality; they shared a keen sense of humour and plenty of laughter.

Their relaxations were picnicking in the country, hill walking, and swimming, generally with a few extra children, and gardening. Charlotte took to oil painting in her middle 40's, giving much pleasure to herself and also to her friends. She was an active member of the Society of Friends. Paul Edwards, Charlotte's husband, was her non-medical partner throughout and especially during the last few years when they did such remarkable work together for physically handicapped children at Lorton Hall. It is good to know that this venture will carry on."

Notes and News

STERILISATION BY STEAM

THE Minister of Health [1] has commended to hospital authorities the report by the Medical Research Council's working party on pressure-steam sterilisers which appeared in these columns in February.[2] The Minister attaches particular importance to the conclusion that the widespread lack of understanding in hospitals of the exact conditions required for efficient sterilisation is due to "the fact that no one member of the medical staff is given the final responsibility of ensuring the provision of suitable equipment and its proper use and control by specially trained operators". The Minister recommends that at each hospital one member of the medical staff—whether a pathologist or a clinician—should be charged with this responsibility.

"The person in question would need to ensure that the staff operating the sterilizers were fully instructed in their duties. He would also need to specify the conditions—of pressure, vacuum, temperature and time—under which the apparatus should be worked so that the hospital engineer could take steps to meet them: and he would be responsible for ensuring that the operating instructions met the necessary requirements. Finally, he would be responsible for arranging for periodical testing of all sterilizers in the hospital to ensure that all material passing through them was effectively sterilized. The hospital engineer should be responsible for ensuring that the engineering services are of the quality required for the particular purpose of the sterilizer and that the mechanical and electrical parts of sterilizers are kept in good working order."

The working party discussed the use of packs in textile, paper, or cardboard containers, instead of drums, and suggested that the advantages of packs far outweighed the disadvantages; but in the Minister's view further experience is desirable before this advice is generally adopted. The working party expressed the opinion that all hospital boilers operating at atmospheric pressure and used for sterilising instruments and utensils should be replaced by pressure-steam sterilisers. "This", says the Minister, "is far-reaching advice, which . . . could only be implemented over a period of time, and one answer to the problem may be to consider the practicability of setting up central sterile supply departments so as to overcome the need for having expensive items of equipment dispersed throughout hospitals."

A MEDICAL PAINTER'S EXHIBITION

IN a one-man show now on display in London,[3] Dr. Phœbus Tuttnauer is revealed as a talented and vivacious painter. His highly colourful pictures positively vibrate on the walls (though the latest work—*Fantasy: The Lake by Moonlight*—is composed in subtler hues). While Dr. Tuttnauer is in his present vein we may enjoy him to the full, for his command over colour ensures no lapse, no garish contrast, no tonal indiscretion; *The Keepers of Paradise* is a lovely example of his control. At times the presentation is highly sophisticated, as in *Boats at Rest* and *The Lonely Robin*, when the reserve and intellect of the elderly man take charge; at other times the boy must out, providing the guileless charm of *Salso Maggiore* (the version in oil), *On Lake Lugano*, and *The New House, Ashford, Kent*. The very dichotomy heightens the pleasure. Only *The Doctor's Workshop 1 and 2* hang dull and heavy on the walls. Perhaps they reflect an unconscious desire to be rid of that tyrant, Medicine, which must prevent the artist spending all his time with the brush. Certainly they lack the sensitivity and charm of the other pictures; it is as though the objects from the surgery are unloved; perhaps Dr. Tuttnauer meant us to feel this.

University of Aberdeen

At a graduation ceremony in July the honorary degree of LL.D. will be conferred on Prof. E. W. H. Cruickshank and Prof. Michael Polanyi.

1. H.M.(59)33.
2. *Lancet*, Feb. 28, 1959, p. 425. A limited number of copies (9*d*. plus 2*d*. postage) may be had from *The Lancet*.
3. At Ben Uri Art Gallery, 11, Portman Street, London, W.1: Mondays to Fridays 10 A.M. to 5 P.M., Sundays 2-5 P.M., until April 21.

British Specialists for Iran

At the request of the Iranian Ministry of Education, the British Council are arranging for British doctors to be attached temporarily to universities in Iran. Dr. J. D. Cumming is leaving this month to spend about six weeks as lecturer in physiology at the University of Meshed. The Council is next arranging lectureships in clinical pathology and biology at Shiraz University.

Royal Australasian College of Surgeons

Alan Newton prize.—The subject chosen for the next award of this prize is the pathology and surgery of hernias of the abdominal wall.

Candidates must hold an Australasian, British, or South African fellowship in surgery, and the closing date for entries is Dec. 1, 1960. Further particulars may be had from the secretary of the college, Spring Street, Melbourne, C.1.

Institute for the Study and Treatment of Delinquency

This institute will hold a conference from May 1 to 3 at Bracklesham Bay Hotel, Sussex, on problems of adoption, and a course on assessing the offender for the courts will be held from May 29 to 31 at Moor Park College, Farnham, Surrey, and from Sept. 14 to 19 at Nottingham University a summer school on crime and punishment. Further particulars may be had from Miss Eve Saville, at the institute, 8, Bourdon Street, London, W.1.

Institution of Mechanical Engineers

A symposium on biomechanics will be held on Friday, April 17, at 4 P.M. at the institution, 1, Birdcage Walk, London, S.W.1. The speakers will include Mr. John Charnley, F.R.C.S., Dr. D. S. McKenzie, and Mr. A. C. Bingold, F.R.C.S. Further particulars may be had from the secretary of the institution.

British Institute of Radiology

On Thursday, April 16, at 8 P.M., at the institute, 32, Welbeck Street, London, W.1, Prof. Gilbert Stead will give the Silvanus Thompson lecture for 1959. His subject will be 1895 And All That.

Medical Art Exhibition at Edinburgh

An art exhibition will be held in Edinburgh during the combined annual meeting of the British and Canadian Medical Associations.

The closing date for entries is April 30. Further particulars may be had from Prof. B. G. Maegraith, School of Tropical Medicine, University of Liverpool, Pembroke Place, Liverpool, 3; Dr. A. M. Rackow, 11, Deepdale, Parkside Avenue, Wimbledon, London, S.W.19; or Prof. D. E. C. Mekie, Royal College of Surgeons, 18, Nicolson Street, Edinburgh, 8.

Colonel J. H. Prain has been appointed honorary physician to the Queen, in succession to Colonel N. C. Oswald, and Colonel R. G. W. Ollerenshaw, honorary surgeon, in succession to Colonel W. H. Wolstenholme.

Owing to rebuilding it will not be possible to hold demonstrations in psychiatry and neurology during the summer term at St. George's Hospital Medical School. They will be resumed in October.

A meeting of the subscribers of the Naval Medical Compassionate Fund will be held on Friday, May 1, at 2.45 P.M., at the Medical Department of the Navy, Queen Anne's Mansions, St. James's Park, London, S.W.1.

The Minister of Health has appointed Mr. A. J. O. Prince as his assistant private secretary, and the Parliamentary Secretary has appointed Miss P. A. Hooper as his private secretary.

An exhibition to be held by the Medical Artists' Association of Great Britain at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, will be opened at 5.30 P.M. on Monday, April 20, and will then be on display from 10 A.M. to 5 P.M. each weekday until Friday, May 1.

A new edition has been published of *Health Services in Britain*, one of the pamphlets prepared by the Central Office of Information for the Overseas Information Services. Copies may be had (3*s.* 6*d.*) from H.M. Stationery Office.

Outlines of General Practice.—This book, reviewed last week in an annotation entitled For Teacher and for Taught, is obtainable from the author, Dr. A. J. Laidlaw, at 29, Barbourne Road, Worcester. For single copies the price, including postage, is 1*s.* 11*d.* (paper cover) or 5*s.* (linen cover).

Diary of the Week

APRIL 12 TO 18

Monday, 13th

ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Nicolson Street, Edinburgh, 8.
5 P.M. Prof. J. H. Louw (Cape Town): Intestinal Malrotation and Duodenal Ileus.

Tuesday, 14th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Prof. E. J. Wayne: Clinical and Metabolic Studies in Thyroid Disease. (First of two Lumleian lectures.)
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. G. L. Bourne: Anatomy, Physiology, and Pathology of the Human Amnion and Chorionic Membranes.
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Psychiatry.* Dr. B. H. Kirman, Dr. J. M. Berg: Ætiology of Mental Defect. Dr. D. W. Kay: Observations on the Natural History and Genetics of Old Age Psychoses.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. Lionel Higgins: Abruptio Placentæ (Accidental Hæmorrhage).
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. G. F. Swann: Encephalography or Ventriculography?

Wednesday, 15th

ROYAL SOCIETY OF MEDICINE
5 P.M. *Comparative Medicine.* Dr. P. R. Lewis, Dr. J. D. Findlay: Adaptations of Man and Animals to Their Environment.
8.15 P.M. *General Practice.* Prof. W. C. W. Nixon, Dr. Jean Mackintosh, Dr. C. W. Walker, Miss A. Wood: The General Practitioner in the Midwifery Services.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8.30 P.M. (Royal Society of Arts, John Adam Street, W.C.2.) Sir Wilson Jameson: Laying the Foundations.
HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.15 P.M. Dr. S. J. Hadfield, Dr. Alistair French: Medical Ethics.
ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, 9, Queen Street, Edinburgh, 2
5 P.M. Mr. T. Holmes Sellors: Contribution of Surgery to Clinical Cardiology. (George Alexander Gibson lecture.)

Thursday, 16th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Professor Wayne: Clinical and Metabolic Studies in Thyroid Disease. (Second of two Lumleian lectures.)
ASSOCIATION OF CLINICAL PATHOLOGISTS
2 P.M. (University of Manchester.) Opening of three-day meeting.
MANCHESTER MEDICAL SOCIETY
8 P.M. (114, Mount Pleasant, Liverpool, 3.) *Anæsthetics.* Dr. I. C. Geddes: Hyperventilation in Anæsthesia. Dr. A. R. Hunter: Experimental and Clinical Observations on Analgesic Drugs.

Friday, 17th

ROYAL SOCIETY OF MEDICINE
8.15 P.M. *Radiology.* Prof. B. W. Windeyer: Chordoma. (Presidential address.)
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. Anthony Radcliffe: Dysphagia.
BRITISH ASSOCIATION OF PHYSICAL MEDICINE
10 A.M. (Guy's Hospital, S.E.1.) Opening of two-day meeting.
BRITISH TUBERCULOSIS ASSOCIATION
11 A.M. (Cardiff Royal Infirmary.) Opening of two-day meeting.
UNIVERSITY OF LIVERPOOL
5.30 P.M. (New Medical School, Ashton Street, Liverpool.) Professor Louw: Neonatal Hirschsprung's Disease.

Appointments

COOPER, FLAVIA Z. L. B., M.B. Brist., D.A.: assistant anæsthetist, Royal Samaritan Hospital for Women, Glasgow.
HAIGH, R. D., M.B. Leeds, M.M.S.A., D.OBST., D.P.H., D.C.H.: M.O.H. and principal school M.O., Lincoln.
JENNINGS, H. C., M.B. Manc.: assistant M.O.H. and assistant school M.O., Oldham.
MCCORMACK, JOHN, M.B. Durh., D.P.H.: deputy M.O.H. and deputy principal school M.O., Lincoln.
MACGREGOR, G. W. R., L.R.C.P.E.: senior assistant M.O.H., Derby.
MILLER, H. R. W., L.R.C.P.E., D.P.H.: assistant divisional M.O., Prestwick area, Lancashire County Council.
ROBERTSON, R. F., M.D. Edin., F.R.C.P.E.: consultant physician, Leith Hospital, Edinburgh.
STEWART, P. D., M.D. Edin.: consultant clinical pathologist, Vale of Leven Hospital, Alexandria, Dunbartonshire.
VAUGHAN, D. H., M.B. Edin., D.P.H.: deputy M.O.H., Salford.
WELLS, G. C., M.B. Cantab., M.R.C.P.: consultant dermatologist, St. John's Hospital for Diseases of the Skin, London.

Manchester Regional Hospital Board:

KELSO, W. M. S., M.B. Glasg., F.R.C.S.E.: senior casualty officer, Preston Royal Infirmary.
SCHILL, ELEANOR B., M.B. Manc., D.P.M.: assistant psychiatrist (S.H.M.O.), Withington Hospital, Manchester.
WINSTON, R. M., M.D., B.SC. Manc.: consultant pathologist, Hope Hospital, Salford.

Births, Marriages, and Deaths

BIRTHS

YOUNG.—On April 1, in Saskatoon, Canada, to Margot, wife of Dr. F. O. Young, a daughter—Janice Nicole